Please type a sign (+) inside this box + PTO/SB/05 (08-00)

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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR § 1 53(b))

Attorney Docket No.	*PF523P1*
First Inventor	*RUBEN et al.*
Title	*Antibodies that Immunospecifically Bind BlyS*
Express Mail Label No.	

jc860 U.S. PTO 06/15/01

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

jc474 U.S. PTO 09/880748 06/15/01

1. ☒ Fee Transmittal Form (*e.g.*, PTO/SB/17) *(Submit an original, and a duplicate for fee processing)*
2. ☐ Applicant claims small entity status. See 37 CFR 1.27.
3. ☒ Specification [Total Pages 358]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross Reference to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to sequence listing, a table, or a computer program listing appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings *(if filed)*
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
4. ☒ Drawing(s) (35 U.S.C. 113) [Total Sheets 16]
5. ☒ Unexecuted Declaration [Total Pages 2]
   a. ☐ Newly executed (original or copy)
   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional with Box 17 completed)*
   i. ☐ DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR §§ 1.63(d)(2) and 1.33(b).
6. ☒ Application Data Sheet. See 37 CFR 1.76.
7. ☐ CD-ROM or CD-R in duplicate, large table or Computer Program *(Appendix)*
8. Nucleotide and/or Amino Acid Sequence Submission *(if applicable, all necessary)*
   a. ☐ Computer Readable Form (CRF)
   b. Specification Sequence Listing on:
      i. ☒ CD-ROM or CD-R (2 copies); or
      ii. ☒ paper
   c. ☒ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ Assignment Papers (cover sheet and document(s))
10. ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
11. ☐ English Translation Document (if applicable)
12. ☐ Information Disclosure Statement/ Form PTO/SB/08
    ☐ Copies of Citations
13. ☐ Preliminary Amendment
14. ☒ Return Receipt Postcard (MPEP 503) (should be specifically itemized)
15. ☐ Certified copy of Priority Document(s) (if foreign priority is claimed)
16. ☐ Other:

17. If a CONTINUING APPLICATION, *check appropriate box, and supply the requisite information below and in a preliminary amendment, or in an Application Data Sheet under 37 CFR 1.76:*

☐ Continuation ☐ Divisional ☐ Continuation-in-Part (CIP) of prior application No: _____,
which claims priority to *Prior application information:* *Examiner* _____ *Group/Art Unit:* _____

Priority of Provisional Application Serial Nos. 60/212,210, filed June 15, 2000; 60/240,816, filed October 17, 2000; 60/276,248, filed March 16, 2001; 60/277,379, filed March 21, 2001, and 60/293,499, filed May 25, 2001, is hereby claimed under 35 U.S.C. §119(e)

For CONTINUATION OR DIVISIONAL APPS only The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts

18. CORRESPONDENCE ADDRESS

☒ ***Customer Number or Bar Code Label*** **22195** *or* ☐ *Correspondence address below*

NAME	Kenley K. Hoover				
	c/o Human Genome Sciences, Inc.				
ADDRESS	9410 Key West Avenue				
CITY	Rockville	*STATE*	MD	*ZIP CODE*	20850
COUNTRY	USA	*TELEPHONE*	301-610-5771	*FAX*	301-309-8439
NAME (Print/Type)	Kenley K. Hoover	*Registration No. (Attorney/Agent)*	40,302		
SIGNATURE				*Date*	

Burden Hour Statement this form is estimated to take 0 2 hours to complete Time will vary depending upon the needs of the individual case Any comments on the amount of time you are required to complete t his form should be sent to the Chief Information Officer, U S Patent and Trademark Office, Washington, DC 20231 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

Complete if Known	
Application Number	Not yet assigned
Filing Date	June 15, 2001
First Named Inventor	RUBEN et al.
Examiner Name	Not yet assigned
Group Art Unit	Not yet assigned
Attorney Docket Number	PF523P1

Total amount of payment	**$2858.00**

METHOD OF PAYMENT

1. ☒ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to:

Deposit Account Number **08-3425**

Deposit Account Name **Human Genome Sciences, Inc.**

☒ Charge Any Additional Fee Required Under 37 CFR §§ 1.16 and 1.17

☐ Applicant claims small entity status. See 37 CFR 1.27

2. ☐ **Payment Enclosed:**

☐ Check ☐ Credit Card ☐ Money Order ☐ Other*

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	710.00
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) **$710.00**

2. EXTRA CLAIM FEES

			Extra Claims	Fee from below	Fee Paid
Total Claims	96	20**	76	$18.00	1368.00
Independent Claims	6	-3*	3	$80.00	240.00
Multiple Dependent			2	$270.00	540.00

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
108	80	209	40	** Reissue independent claims over original patent
110	18	210	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) **$2148.00**

** *or number previously paid, if greater, For Reissues, see above*

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Fee Code	Large Entity Fee ($)	Fee Cod	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive -unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1.240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Statement	
581	40	481	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR 1 129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR 1 129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify):					
Other fee (specify):					
Other fee (specify):					

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) **$0.00**

Submitted By Complete *(if applicable)*

Name *(Print/Type)* Kenley K. Hoover	Registration No.: 40,302	Telephone	301-610-5771
Signature:		Date: June 15, 2001	

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ANTIBODIES THAT IMMUNOSPECIFICALLY BIND TO BLyS

INTRODUCTION

[001] The present invention relates to antibodies and related molecules that immunospecifically bind to BLyS. The present invention also relates to methods and compositions for detecting, diagnosing, or prognosing a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor, comprising antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS. The present invention further relates to methods and compositions for preventing, treating or ameliorating a disease or disorder associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS function or BLyS receptor function, comprising administering to an animal, preferably a human, an effective amount of one or more antibodies or fragments or variants thereof, or related molecules, that immunospecifically bind to BLyS.

BACKGROUND OF THE INVENTION

[002] B lymphocyte stimulator (BLyS) is a member of the tumor necrosis factor ("TNF") superfamily that induces both *in vivo* and *in vitro* B cell proliferation and differentiation (Moore *et al.*, Science 285: 260-263 (1999)). BLyS is distinguishable from other B cell growth and differentiation factors such as IL-2, IL-4, IL-5, IL-6, IL-7, IL-13, IL-15, CD40L, or CD27L (CD70) by its monocyte-specific gene and protein expression pattern and its specific receptor distribution and biological activity on B lymphocytes. BLyS expression is not detected on natural killer ("NK") cells, T cells or B cells, but is restricted to cells of myeloid origin. BLyS expression on resting monocytes is upregulated by interferon-gamma (IFN-gamma). The gene encoding BLyS has been mapped to chromosome 13q34.

[003] BLyS is expressed as a 285 amino acid type II membrane-bound polypeptide and a soluble 152 amino acid polypeptide (Moore *et al.*, 1999 *supra*). The membrane-bound form of BLyS has a predicted transmembrane spanning domain between amino acid residues 47 and 73. The NH_2-terminus of the soluble form of BLyS

begins at Ala^{134} of the membrane-bound form of BLyS. Soluble recombinant BLyS has been shown to induce *in vitro* proliferation of murine splenic B cells and to bind to a cell-surface receptor on these cells (Moore *et al.*, 1999 *supra*). Soluble BLyS administration to mice has been shown to result in an increase in the proportion of $CD45R^{dull}$, $Ly6D^{bright}$ (also known as ThB) B cells and an increase in serum IgM and IgA levels (Moore *et al.*, 1999 *supra*). Thus, BLyS displays a B cell tropism in both its receptor distribution and biological activity.

[004] Based upon its expression pattern and biological activity, BLyS has been suggested to be involved in the exchange of signals between B cells and monocytes or their differentiated progeny. The restricted expression patterns of BLyS receptor and ligand suggest that BLyS may function as a regulator of T cell-independent responses in a manner analogous to that of CD40 and CD40L in T cell-dependent antigen activation. As such, antibodies and related molecules that immunospecifically bind to BLyS may find medical utility in, for example, the treatment of B cell disorders associated with autoimmunity, neoplasia, or immunodeficiency syndromes.

SUMMARY OF THE INVENTION

[005] The present invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS. In particular, the invention encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes), preferably human BLyS. The present invention also encompasses methods and compositions for detecting, diagnosing, or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate function of

BLyS or BLyS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, use of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be detected, diagnosed, or prognosed with the antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma). The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate function of BLyS or BLyS receptor in an animal, preferably a mammal, and most preferably a human, comprising, or alternatively consisting of, administering to said animal an effective amount of one or more antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or ameliorated by administering an effective amount of an antibody of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[006] Using phage display technology, the present inventors have identified single chain antibody molecules ("scFvs") that immunospecifically bind to BLyS, including scFvs that immunospecifically bind to soluble BLyS, scFvs that immunospecifically bind the membrane-bound form of BLyS, and scFvs that immunospecifically bind to both the soluble form and the membrane-bound form of BLyS. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the

soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[007] In particular, the invention relates to scFvs comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of SEQ ID NOS: 1 – 2128, preferably SEQ ID NOS:834 - 872, 1570 - 1595, and 1886 – 1908, and most preferably SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, and 1881 - 1885, as referred to in Table 1 below. In specific embodiments, the present invention relates to scFvs that immunospecifically bind the soluble form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1569, preferably SEQ ID NOS:1570 - 1595, and most preferably SEQ ID NOS: 1563 – 1569, as referred to in Table 1, below. In other embodiments, the present invention also relates to scFvs that immunospecifically bind the membrane-bound form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128, preferably SEQ ID NOS:1886 - 1908, and most preferably SEQ ID NOS: 1881 - 1885, as referred to in Table 1 below. The present invention further relates to scFvs that immunospecifically bind both the membrane-bound form and soluble form of BLyS, said scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562, preferably SEQ ID NOS: 834 - 872, and most preferably SEQ ID NOS: 1 – 46, and 321 - 329, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these scFvs, and/or molecules.

[008] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the variable heavy ("VH") domains referred to in Table 1, below, or any one of the variable light ("VL") domains referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a

polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. In another preferred embodiment, antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of a VL domain contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as referred to in Table 1 below. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[009] The present invention also provides antibodies (including molecules comprising or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1, below, and any one of the VL domains referred to in Table 1. In a preferred embodiment, the antibodies of the invention comprise or alternatively consist of, a polypeptide having the amino acid sequence of a VH and VL domain contained in the same scFv referred to in Table 1. In another preferred embodiment, antibodies of the present invention, comprise, or alternatively consist of, a VH domain from an scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1, and a VL domain from an scFv SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, the VH and VL domain from a single scFv of SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 - 1908, as disclosed in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the

soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[010] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to a polypeptide or a polypeptide fragment of BLyS, said antibodies comprising, or alternatively consisting of, a polypeptide having the amino acid sequence of any one, two, three or more of the VH complementarity determining regions ("CDRs") (*i.e.*, VH CDR1, VH CDR2, or VH CDR3) referred to in Table 1 and/or any one, two, three or more of the VL CDRs (*i.e.*, VL CDR1, VL CDR2, or VL CDR3) referred to in Table 1. In one embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1 and/or any one of the VL CDR1s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR2s referred to in Table 1 and/or any one of the VL CDR2s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR3s referred to in Table 1 and/or any one of the VL CDR3s referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[011] In another embodiment, antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) immunospecifically bind to a polypeptide or polypeptide fragment of BLyS, and comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VH CDR1s referred to in Table 1, any one of the VH CDR2s referred to in Table 1, and/or any one of the VH CDR3s referred to in Table 1. In another embodiment, antibodies of the present invention comprise, or alternatively consist of, a polypeptide having the amino acid sequence of any one of the VL CDR1s referred to in Table 1, any

one of the VL CDR2s referred to in Table 1, and/or any one of the VL CDR3s referred to in Table 1. In a preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, at least one, two, three, four, five, six, or more CDRs that correspond to the same scFv referred to in Table 1, more preferably where CDR1, CDR2, and CDR3 of the VL domain correspond to the same scFv or where CDR1, CDR2, and CDR3 of the VH domain correspond to the same scFv, and most preferably where all six CDRs correspond to the same scFv referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[012] The present invention also provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that: immunospecifically bind to the soluble form of BLyS (e.g., a polypeptide consisting of amino acids 134 - 285 of SEQ ID NO:3228); that immunospecifically bind to the membrane-bound form of BLyS (e.g., a polypeptide consisting of amino acids 1 - 285 of SEQ ID NO:3228 or a BLyS polypeptide expressed on the surface of monocytes) and/or that immunospecifically bind to both the soluble form and membrane-bound form of BLyS. In a preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the soluble form of BLyS. In another preferred embodiment, antibodies of the present invention immunospecifically bind to the membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL CDR3 corresponding to one or more scFvs, that immunospecifically bind to the membrane-bound form of BLyS. In yet another preferred embodiment, antibodies of the present invention immunospecifically bind to the soluble form and membrane-bound form of BLyS and comprise, or alternatively consist of, a VH domain, VH CDR1, VH CDR2, VH CDR3, VL domain, VL CDR1, VL CDR2, and/or VL

CDR3 corresponding to one or more scFvs, that immunospecifically binds to the soluble form and membrane-bound form of BLyS. In another preferred embodiment, antibodies of the present invention comprise, or alternatively consist of, a VH domain and a VL domain corresponding to the same scFv disclosed in Table 1, which antibodies immunospecifically bind to the soluble form of BLyS, the membrane-bound form of BLyS, or both the soluble form and membrane-bound form of BLyS. Nucleic acid molecules encoding these antibodies are also encompassed by the invention. Molecules comprising, or alternatively consisting of, fragments or variants of these antibodies (e.g., including VH domains, VH CDRs, VL domains, or VL CDRs having an amino acid sequence of any one of those referred to in Table 1), that immunospecifically bind the soluble form of BLyS, the membrane-bound form of BLyS, and/or both the soluble form and membrane-bound form of BLyS, are also encompassed by the invention, as are nucleic acid molecules that encode these antibodies, and/or molecules.

[013] A VH domain of an amino acid sequence disclosed herein may be combined with

[014] a VL domain of an amino acid sequence disclosed herein, or other VL domains, to provide a VH/VL pairing representing an antigen-binding site of an antibody. Similarly, a VL domain of an amino acid sequence disclosed herein may be combined with a VH domain of an amino acid sequence disclosed herein, or other VH domains. Further, one or more CDRs disclosed herein may be taken from a VH or VL domain and incorporated into a suitable framework as discussed *infra*.

[015] The present invention provides antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof (including derivatives)) comprising, or alternatively consisting of, of VH domains, VL domains and/or CDRs described herein, which antibodies, immunospecifically bind to BLyS (e.g., soluble BLyS and membrane-bound BLyS) and can be routinely assayed for immunospecific binding to BLyS using methods known in the art, such as, for example, the immunoassays disclosed *infra*. Antibodies and antibody fragments or variants (including derivatives) of the invention may include, for example, one or more amino acid sequence alterations (addition, deletion, substitution and/or insertion of an amino acid residue). These alterations may be made in one or more framework regions and/or one or more CDR's. The antibodies of the invention (including antibody fragments, and variants

and derivative thereof) can be routinely made by methods known in the art. Molecules comprising, or alternatively consisting of, fragments or variants of any of the VH domains, VH CDRs, VL domains, and VL CDRs whose sequences are specifically disclosed herein may be employed in accordance with the present invention. Nucleic acid molecules encoding these antibodies and molecules (including fragments, variants, and derivatives) are also encompassed by the invention.

[016] The present invention also provides panels of antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants) wherein the panel members correspond to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, $F(ab')_2$ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs). The present invention further provides mixtures of antibodies, wherein the mixture corresponds to one, two, three, four, five, ten, fifteen, twenty, or more different antibodies of the invention (e.g., whole antibodies, Fabs, $F(ab')_2$ fragments, Fd fragments, disulfide-linked Fvs (sdFvs), antiidiotypic (anti-Id) antibodies, and scFvs)). The present invention also provides for compositions comprising, or alternatively consisting of, one, two, three, four, five, ten, fifteen, twenty, or more antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). A composition of the invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty, or more amino acid sequences of one or more antibodies or fragments or variants thereof. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one or more antibodies of the invention.

[017] The present invention also provides for fusion proteins comprising an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) of the invention, and a heterologous polypeptide (*i.e.*, a polypeptide unrelated to an antibody or antibody domain). Nucleic acid molecules encoding these fusion proteins are also encompassed by the invention. A composition of the present invention may comprise, or alternatively consist of, one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the invention. Alternatively, a composition of the invention may comprise, or alternatively consist of, nucleic acid molecules encoding one, two, three, four, five, ten, fifteen, twenty or more fusion proteins of the

invention.

[018] The present invention also provides for a nucleic acid molecule, generally

[019] isolated, encoding an antibody (including molecules such as scFvs, which comprise, or alternatively consist of, an antibody fragment or variant thereof) of the invention. The present invention also provides a host cell transformed with a nucleic acid molecule of the invention and progeny thereof. The present invention also provides a method for the production of an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention. The present invention further provides a method of expressing an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof) of the invention from a nucleic acid molecule. These and other aspects of the invention are described in further detail below.

[020] The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[021] In specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiencies). In other specific embodiments, the present invention encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency).

[022] The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal,

preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[023] In specific embodiments, the present invention encompasses methods and compositions (e.g., antagonistic anti-BLyS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypergammaglobulinemia (e.g., AIDS, autoimmune diseases, and some immunodeficiency syndromes). In other specific embodiments, the present invention encompasses methods and compositions (e.g., agonistic anti-BLyS antibodies) for preventing, treating or ameliorating diseases or disorders associated with hypogammaglobulinemia (e.g., an immunodeficiency syndrome).

[024] Autoimmune disorders, diseases, or conditions that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmune neutropenia, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, gluten-sensitive enteropathy, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g., IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, myocarditis, IgA glomerulonephritis, dense deposit disease, rheumatic heart disease, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erhythematosus, discoid lupus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease , (b) Myasthenia Gravis, and (c)

insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura , rheumatoid arthritis, schleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjögren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiotomy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders).

[025] Immunodeficiencies that may be detected, diagnosed, prognosed, or monitored using the antibodies of the invention include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVID) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic alymphoplasia-aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

DEFINITIONS

[026] The term "antibody," as used herein, refers to immunoglobulin molecules

and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that immunospecifically binds an antigen. As such, the term antibody encompasses not only whole antibody molecules, but also antibody fragments as well as variants (including derivatives) of antibodies and antibody fragments. Examples of molecules which are described by the term "antibody" in this application include, but are not limited to: single chain Fvs (scFvs), Fab fragments, Fab' fragments, $F(ab')_2$, disulfide linked Fvs (sdFvs), Fvs, and fragments comprising or alternatively consisting of, either a VL or a VH domain. The term "single chain Fv" or "scFv" as used herein refers to a polypeptide comprising a VL domain of antibody linked to a VH domain of an antibody. Antibodies that immunospecifically bind to BLyS may have cross-reactivity with other antigens. Preferably, antibodies that immunospecifically bind to BLyS do not cross-react with other antigens. Antibodies that immunospecifically bind to BLyS can be identified, for example, by immunoassays or other techniques known to those of skill in the art, *e.g.*, the immunoassays described in the Examples below.

[027] Antibodies of the invention include, but are not limited to, monoclonal, multispecific, human or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, antiidiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The immunoglobulin molecules of the invention can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA and IgY), class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2) or subclass of immunoglobulin molecule.

[028] Preferably, an antibody of the invention comprises, or alternatively consists of, a VH domain, VH CDR, VL domain, or VL CDR having an amino acid sequence of any one of those referred to in Table 1, or a fragment or variant thereof.

[029] An antibody of the invention "which binds the soluble form of BLyS" is one which binds the 152 amino acid soluble form of the BLyS protein (amino acids 134-285 of SEQ ID NO:3228). In specific embodiments of the invention, an antibody of the invention "which binds the soluble form of BLyS" does not also bind the membrane-bound or membrane-associated form of BLyS. Assays which measure binding to the soluble form of BLyS include, but are not limited to, receptor binding inhibition assay or capture of soluble BLyS from solution as described in Examples 8 and 9.

[030] An antibody of the invention "which binds the membrane-bound form of

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Phe Asp Tyr

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<213> Homo sapiens

<400> 2757
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1 5 10 15

<210> 2758
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<212> PRT
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<400> 2758
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1 5 10 15

Asp Tyr

<210> 2759
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1 5 10 15

Phe Asp Ile

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1 5 10 15

<210> 2761
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<210> 2762
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Asp Val

<210> 2763
<211> 21
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Tyr Gly Met Asp Val
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<400> 2765
Ala Arg Arg Val Gly Val Leu Gly Gly Lys Asn Ala Phe Glu Ile
1 5 10 15

<210> 2766
<211> 18
<212> PRT
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<400> 2766
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1 5 10 15

Asp Tyr

<210> 2767
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Gln Lys Val Tyr Tyr Asp Ile Leu Thr Gly Tyr Asn Tyr Tyr Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> 2768
<211> 14
<212> PRT
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<400> 2768
Glu Gly Ala Ala Asp Tyr Leu Asn Gly Gln Tyr Phe Gln Asp
1 5 10

<210> 2769

of the BLyS polypeptides of the invention, their preparation, and compositions (preferably, pharmaceutical compositions) containing them. In specific embodiments, the antibodies of the invention bind BLyS monomers, dimers, trimers or tetramers. In additional embodiments, the antibodies of the invention bind at least dimers, at least trimers, or at least tetramers of BLyS.

[061] Multimeric BLyS bound by the antibodies of the invention may be homomers or heteromers. A BLyS homomer, refers to a multimer containing only BLyS polypeptides (including BLyS fragments, variants, and fusion proteins, as described herein). These homomers may contain BLyS polypeptides having identical or different amino acid sequences. In specific embodiments, the antibodies of the invention bind a BLyS homodimer (e.g., containing two BLyS polypeptides having identical or different amino acid sequences) or a BLyS homotrimer (e.g., containing three BLyS polypeptides having identical or different amino acid sequences). In a preferred embodiment, the antibodies of the invention bind homotrimers of BLyS. In additional embodiments, the antibodies of the invention bind a homomeric BLyS multimer which is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[062] Heteromeric BLyS refers to a multimer containing heterologous polypeptides (i.e., polypeptides of a different protein) in addition to the BLyS polypeptides of the invention. In a specific embodiment, the antibodies of the invention bind a BLyS heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the antibodies of the invention bind a heteromeric BLyS multimer which is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer. In highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising both BLyS polypeptides and APRIL polypeptides (SEQ ID NO:3239; GenBank Accession No. AF046888; PCT International Publication Number WO97/33902; J. Exp. Med. 188(6):1185-1190) or fragments or variants thereof. In other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising one BLyS polypeptide (including fragments or variants) and two APRIL polypeptides (including fragments or variants). In still other highly preferred embodiments, the antibodies of the invention bind a heterotrimer comprising two BLyS polypeptides (including fragments or variants) and one APRIL polypeptide (including fragments or variants). In a further nonexclusive embodiment, the heteromers bound by the antibodies of the invention

contain CD40 ligand polypeptide sequence(s), or biologically active fragment(s) or variant(s) thereof.

[063] In particularly preferred embodiments, the antibodies of the invention bind homomeric, especially homotrimeric, BLyS polypeptides, wherein the individual protein components of the multimers consist of the mature form of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof. In other specific embodiments, antibodies of the invention bind heteromeric, especially heterotrimeric, BLyS polypeptides such as a heterotrimer containing two BLyS polypeptides and one APRIL polypeptide or a heterotrimer containing one BLyS polypeptide and two APRIL polypeptides, and wherein the individual protein components of the BLyS heteromer consist of the mature extracellular soluble portion of either BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228, or amino acids residues 134-266 of SEQ ID NO:3229) or fragments or variants thereof, or the mature extracellular soluble portion APRIL (e.g., amino acid residues 105-250 of SEQ ID NO:3239) or fragments or variants thereof.

[064] In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS monomeric protein. In specific embodiments, the antibodies of the invention bind conformational epitopes of a BLyS multimeric, especially trimeric, protein. In other embodiments, antibodies of the invention bind conformational epitopes that arise from the juxtaposition of BLyS with a heterologous polypeptide, such as might be present when BLyS forms heterotrimers (e.g., with APRIL polypeptides (e.g., SEQ ID SEQ ID NO:3239)), or in fusion proteins between BLyS and a heterologous polypeptide.

[065] BLyS multimers bound by the antibodies of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, BLyS multimers, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, BLyS heteromultimers, such as, for example, BLyS heterotrimers or BLyS heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, BLyS multimers are formed

by covalent associations with and/or between the BLyS polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:3228 or SEQ ID NO:3229). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a BLyS fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a BLyS-Fc fusion protein. In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another TNF family ligand/receptor member that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication No. WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from CD40L, or a soluble fragment thereof. In another embodiment, two or BLyS polypeptides are joined through synthetic linkers (e.g., peptide, carbohydrate or soluble polymer linkers). Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple BLyS polypeptides separated by peptide linkers may be produced using conventional recombinant DNA technology.

[066] In one embodiment, antibodies of the invention immunospecifically bind a BLyS polypeptide having the amino acid sequence of SEQ ID NO:3228 or as encoded by the cDNA clone contained in ATCC No. 97768, or a polypeptide comprising a portion (i.e., a fragment) of the above polypeptides. In another embodiment, the invention provides an antibody that binds an isolated BLyS polypeptide having the amino acid sequence of SEQ ID NO:3229 or the amino acid sequence encoded by the cDNA clone contained in ATCC No. 203518, or a an antibody that binds polypeptide comprising a portion (i.e, fragment) of the above polypeptides.

[067] Antibodies of the present invention immunospecifically bind to

polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3228, encoded by the cDNA contained in the plasmid having ATCC accession number 97768, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[068] Additionally, antibodies of the present invention bind polypeptides comprising or alternatively, consisting of, the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Antibodies of the present invention also bind to fragments of the amino acid sequence of SEQ ID NO:3229, encoded by the cDNA contained in the plasmid having ATCC accession number 203518, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone.

[069] In addition, antibodies of the invention bind polypeptides or polypeptide fragments comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NOS: 3230 through 3237.

[070] In specific embodiments, the antibodies of the present invention immunospecifically bind polypeptide fragments including polypeptides comprising or alternatively, consisting of, an amino acid sequence contained in SEQ ID NO:3228, encoded by the cDNA contained in the deposited clone, or encoded by nucleic acids which hybridize (e.g., under stringent hybridization conditions) to the nucleotide sequence contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by the antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 50, 51 to 100, 101 to 150, 151 to 200, 201 to 250, and/or 251 to 285 of SEQ ID NO:3228. Moreover,

polypeptide fragments can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino acids in length.

[071] In specific embodiments, antibodies of the present invention bind polypeptide fragments comprising, or alternatively consisting of, amino acid residues: 1-46, 31-44, 47-72, 73-285, 73-83, 94-102, 148-152, 166-181, 185-209, 210-221, 226-237, 244-249, 253-265, and/or 277-285 of SEQ ID NO:3228.

[072] It will be recognized by one of ordinary skill in the art that mutations targeted to regions of a BLyS polypeptide of SEQ ID NO:3228 which encompass the nineteen amino acid residue insertion which is not found in the BLyS polypeptide sequence of SEQ ID NO:3229 (i.e., amino acid residues Val-142 through Lys-160 of the sequence of SEQ ID NO:3229) may affect the observed biological activities of the BLyS polypeptide. More specifically, a partial, non-limiting and non-exclusive list of such residues of the BLyS polypeptide sequence which may be targeted for mutation includes the following amino acid residues of the BLyS polypeptide sequence as shown in SEQ ID NO:3228: V-142; T-143; Q-144; D-145; C-146; L-147; Q-148; L-149; I-150; A-151; D-152; S-153; E-154; T-155; P-156; T-157; I-158; Q-159; and K-160. Thus, in specific embodiments, antibodies of the present invention that bind BLyS polypeptides which have one or more mutations in the region from V-142 through K-160 of SEQ ID NO:3228 are contemplated.

[073] Polypeptide fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 15, 16-30, 31-46, 47-55, 56-72, 73-104, 105-163, 163-188, 186-210 and 210-284 of the amino acid sequence disclosed in SEQ ID NO:3228. Additional representative examples of polypeptide fragments that may be bound by antibodies of the present invention, include, for example, fragments that comprise or alternatively, consist of from about amino acid residues: 1 to 143, 1-150, 47-143, 47-150, 73-143, 73-150, 100-150, 140-145, 142-148, 140-150, 140-200, 140-225, and 140-266 of the amino acid sequence disclosed in SEQ ID NO:3229. Moreover, polypeptide fragments that may be bound by antibodies of the present invention, can be at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 175 or 200 amino

acids in length. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini.

[074] Additional preferred embodiments encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (e.g., amino acid residues 1-46 of SEQ ID NO:3228), the predicted transmembrane domain of BLyS (e.g., amino acid residues 47-72 of SEQ ID NO:3228), the predicted extracellular domain of BLyS (e.g., amino acid residues 73-285 of SEQ ID NO:3228), the mature soluble extracellular domain of BLyS (e.g., amino acids residues 134-285 of SEQ ID NO:3228), the predicted TNF conserved domain of BLyS (e.g., amino acids 191 to 284 of SEQ ID NO:3228), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-285 of SEQ ID NO:3228).

[075] Further additional preferred embodiments encompass polypeptide fragments comprising, or alternatively consisting of, the predicted intracellular domain of BLyS (amino acid residues 1-46 of SEQ ID NO:3229), the predicted transmembrane domain of BLyS (amino acid residues 47-72 of SEQ ID NO:3229), the predicted extracellular domain of BLyS (amino acid residues 73-266 of SEQ ID NO:3229), the predicted TNF conserved domain of BLyS (amino acids 172 to 265 of SEQ ID NO:3229), and a polypeptide comprising, or alternatively, consisting of the predicted intracellular domain fused to the predicted extracellular domain of BLyS (amino acid residues 1-46 fused to amino acid residues 73-266 of SEQ ID NO:3229).

[076] Certain additional embodiments of the invention encompass antibodies that bind polypeptide fragments comprising, or alternatively consisting of, the predicted beta-pleated sheet regions of the BLyS polypeptides of SEQ ID NO:3228 and SEQ ID NO:3229. These polypeptide fragments comprising the beta-pleated sheets of BLyS comprise, or alternatively consist of, amino acid residues Gln-144 to Ala-151, Phe-172 to Lys-173, Ala-177 to Glu-179, Asn-183 to Ile-185, Gly-191 to Lys-204, His-210 to Val-219, Leu-226 to Pro-237, Asn-242 to Ala-251, Gly-256 to Ile-263 and/or Val-276 to Leu-284 of SEQ ID NO:3228. In another, nonexclusive embodiment, these polypeptide fragments comprising the beta-pleated sheets of BLyS comprise, or alternatively consist

of, amino acid residues Phe-153 to Lys-154, Ala-158 to Glu-160, Asn-164 to Ile-166, Gly-172 to Lys-185, His-191 to Val-200, Leu-207 to Pro-218, Asn-223 to Ala-232, Gly-237 to Ile-244 and/or Val-257 to Leu-265 of SEQ ID NO:3229.

[077] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences of the invention includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228. Other combinations of amino acids sequences that may be bound by the antibodies of the invention may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-199 to Ala-248] fused to [Gly-249 to Leu-285] fused to [Val-142 to Lys-160] of (SEQ ID NO:3228). Other combinations of amino acids sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Val-142 to Lys-160] fused to [Gly-161 to Gln-198] fused to [Gly-249 to Leu-285] of SEQ ID NO:3228 fused to a FLAG tag ; or [Met-1 to Lys-113] of SEQ ID NO:3228 fused to [Leu-114 to Thr-141] of SEQ ID NO:3228 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Val-142 to Lys-160] of SEQ ID NO:3228 fused to [Gly-161 to Gln-198] of SEQ ID NO:3228 fused to [Val-199 to Ala-248] of SEQ ID NO:3228 fused to [Gly-249 to Leu-285] of SEQ ID NO:3228).

[078] A partial, non-limiting, and exemplary list of polypeptides that may be bound by the antibodies of the invention includes polypeptides that comprise, or alternatively consist of, combinations of amino acid sequences includes, for example, [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; [Met-1 to Lys-113] fused to [Gly-142 to Gln-179] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229; or [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused

to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229. Other of amino acids sequences that may be bound by the antibodies of the invention combinations may include the polypeptide fragments in an order other than that recited above (e.g., [Leu-114 to Thr-141] fused to [Val-180 to Ala-229] fused to [Gly-230 to Leu-266] fused to [Gly-142 to Gln-179] of SEQ ID NO:3229). Other combinations of amino acid sequences that may be bound by the antibodies of the invention may also include heterologous polypeptide fragments as described herein and/or other polypeptides or polypeptide fragments of the present invention (e.g., [Met-1 to Lys-113] fused to [Leu-114 to Thr-141] fused to [Gly-142 to Gln-179] fused to [Gly-230 to Leu-266] of SEQ ID NO:3229 fused to a FLAG tag (SEQ ID NO:3238) or, [Met-1 to Lys-113] of SEQ ID NO:3229 fused to [Leu-114 to Thr-141] of SEQ ID NO:3229 fused to [Glu-135 to Asn-165] of SEQ ID NO:39 fused to [Gly-142 to Gln-179] of SEQ ID NO:3229 fused to [Val-180 to Ala-229] of SEQ ID NO:3229 fused to [Gly-230 to Leu-266] of SEQ ID NO:3229.

[079] Additional embodiments of the invention encompass antibodies that bind BLyS polypeptide fragments comprising, or alternatively consisting of, functional regions of polypeptides of the invention, such as the Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index set out in Tables 9 and 10 and as described herein. In a preferred embodiment, the polypeptide fragments bound by the antibodies of the invention are antigenic (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of a complete (i.e., full-length) BLyS polypeptide (e.g., SEQ ID NOS:3228 and 3229).

[080] The data representing the structural or functional attributes of the BLyS polypeptide of SEQ ID NO:3228 (Table 9) or the BLyS polypeptide of SEQ ID NO:3229 (Table 10), as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. Column I represents the results of a Garnier-Robson analysis of alpha helical regions; Column II represents the results of a Chou-Fasman analysis of alpha helical regions; Column III represents the results of a Garnier Robson analysis of beta sheet regions; Column IV represents the results of a

Chou-Fasman analysis of beta sheet regions; Column V represents the results of a Garnier Robson analysis of turn regions; Column VI represents the results of a Chou-Fasman analysis of turn regions; Column VII represents the results of a Garnier Robson analysis of coil regions; Column VIII represents a Kyte-Doolittle hydrophilicity plot; Column IX represents a Hopp-Woods hydrophobicity plot; Column X represents the results of an Eisenberg analysis of alpha amphipathic regions; Column XI represents the results of an Eisenberg analysis of beta amphipathic regions; Column XII represents the results of a Karplus-Schultz analysis of flexible regions; Column XIII represents the Jameson-Wolf antigenic index score; and Column XIV represents the Emini surface probability plot.

[081] In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Tables 9 and 10 can be used to determine regions of the BLyS polypeptide of SEQ ID NO:3228 (Table 9) or the BLyS polypeptide of SEQ ID NO:3229 (Table 10) which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[082] The above-mentioned preferred regions set out in Tables 9 and 10 include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in SEQ ID NO:2. As set out in Tables 9 and 10, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Jameson-Wolf regions of high antigenic index and Emini surface-forming regions. Preferably, antibodies of the present invention bind BLyS polypeptides or BLyS polypeptide fragments and variants comprising regions of BLyS that combine several structural features, such as several (e.g., 1, 2, 3 , or 4) of the same or different region features set out above and in Tables 9 and 10.

Table 9

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	0.73	-0.71	.	.	.	0.95	1.39
Asp	2	A	.	.	.	.	T	.	1.12	-0.66	*	.	.	1.15	1.56
Asp	3	A	.	.	.	.	T	.	1.62	-1.09	*	.	.	1.15	2.12
Ser	4	A	.	.	.	.	T	.	2.01	-1.51	.	.	.	1.15	4.19
Thr	5	A	.	.	.	.	T	.	2.40	-2.13	.	.	F	1.30	4.35
Glu	6	A	A	.	.	.	.	.	2.70	-1.73	*	*	F	0.90	4.51
Arg	7	A	A	.	.	.	.	.	2.81	-1.34	*	*	F	0.90	4.51
Glu	8	A	A	.	.	.	.	.	2.00	-1.73	*	*	F	0.90	6.12
Gln	9	A	A	.	.	.	.	.	1.99	-1.53	*	*	F	0.90	2.91
Ser	10	A	.	.	B	.	.	.	2.00	-1.04	*	*	F	0.90	2.15
Arg	11	A	.	.	B	.	.	.	1.33	-0.66	*	*	F	0.90	1.66
Leu	12	A	.	.	B	.	.	.	0.41	-0.09	*	*	F	0.45	0.51
Thr	13	A	.	.	B	.	.	.	0.46	0.20	*	*	F	-0.15	0.32
Ser	14	A	A	.	.	.	.	.	0.50	-0.19	*	*	.	0.30	0.32
Cys	15	A	A	.	.	.	.	.	0.91	-0.19	*	*	.	0.30	0.78
Leu	16	A	A	.	.	.	.	.	0.80	-0.87	*	*	F	0.90	1.06
Lys	17	A	A	.	.	.	.	.	1.61	-1.36	.	*	F	0.90	1.37
Lys	18	A	A	.	.	.	.	.	1.32	-1.74	.	*	F	0.90	4.44
Arg	19	A	A	.	.	.	.	.	1.67	-1.70	.	*	F	0.90	5.33
Glu	20	A	A	.	.	.	.	.	1.52	-2.39	.	*	F	0.90	5.33
Glu	21	A	A	.	.	.	.	.	2.38	-1.70	.	*	F	0.90	2.20
Met	22	A	A	.	.	.	.	.	2.33	-1.70	.	*	F	0.90	2.24
Lys	23	A	A	.	.	.	.	.	1.62	-1.70	*	*	F	0.90	2.24
Leu	24	A	A	.	.	.	.	.	0.66	-1.13	*	*	F	0.75	0.69
Lys	25	A	A	.	.	.	.	.	0.36	-0.49	.	*	F	0.45	0.52
Glu	26	A	A	.	B	.	.	.	-0.53	-0.71	*	*	.	0.60	0.35
Cys	27	A	A	.	B	.	.	.	-0.74	-0.03	*	*	.	0.30	0.30
Val	28	A	A	.	B	.	.	.	-1.00	-0.03	*	*	.	0.30	0.12
Ser	29	A	A	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.11
Ile	30	A	.	.	B	.	.	.	-0.08	0.40	*	*	.	-0.30	0.40
Leu	31	A	.	.	B	.	.	.	-0.08	-0.17	*	.	.	0.45	1.08
Pro	32	.	.	.	B	.	.	C	0.29	-0.81	*	.	F	1.10	1.39
Arg	33	.	.	.	.	T	.	.	0.93	-0.81	.	*	F	1.50	2.66
Lys	34	.	.	.	.	T	.	.	0.93	-1.07	.	.	F	1.84	4.98
Glu	35	.	.	.	.	.	.	C	0.97	-1.37	*	*	F	1.98	4.32
Ser	36	.	.	.	.	.	T	C	1.89	-1.16	*	*	F	2.52	1.64
Pro	37	.	.	.	.	.	T	C	1.80	-1.16	*	*	F	2.86	1.60
Ser	38	.	.	.	.	T	T	.	1.39	-0.77	*	.	F	3.40	1.24
Val	39	A	.	.	.	.	T	.	1.39	-0.39	.	*	F	2.36	1.24
Arg	40	A	.	.	.	.	.	.	1.39	-0.77	*	*	F	2.46	1.60
Ser	41	A	.	.	.	.	.	.	1.34	-1.20	*	*	F	2.46	2.00
Ser	42	.	.	.	.	T	T	.	1.60	-1.16	.	*	F	3.06	2.67
Lys	43	.	.	.	.	T	T	.	1.09	-1.80	.	*	F	3.06	2.72
Asp	44	.	.	.	.	T	T	.	1.13	-1.11	*	*	F	3.40	1.67
Gly	45	A	.	.	.	.	T	.	0.43	-0.81	*	*	F	2.66	1.03
Lys	46	A	A	.	.	.	.	.	0.14	-0.70	.	.	F	1.77	0.52
Leu	47	A	A	.	.	.	.	.	0.13	-0.20	*	.	.	0.98	0.31
Leu	48	A	A	.	.	.	.	.	-0.72	0.29	*	.	.	0.04	0.46
Ala	49	A	A	.	.	.	.	.	-1.53	0.54	.	*	.	-0.60	0.19
Ala	50	A	A	.	.	.	.	.	-2.00	1.23	.	.	.	-0.60	0.19

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Thr	51	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.19
Leu	52	A	A	.	.	.	.	.	-2.63	1.04	.	.	.	-0.60	0.19
Leu	53	A	A	.	.	.	.	.	-2.63	1.23	.	.	.	-0.60	0.15
Leu	54	A	A	.	.	.	.	.	-2.34	1.41	.	.	.	-0.60	0.09
Ala	55	A	A	.	.	.	.	.	-2.42	1.31	.	.	.	-0.60	0.14
Leu	56	A	A	.	.	.	.	.	-2.78	1.20	.	.	.	-0.60	0.09
Leu	57	A	.	.	.	.	T	.	-2.78	1.09	.	.	.	-0.20	0.06
Ser	58	A	.	.	.	.	T	.	-2.28	1.09	.	.	.	-0.20	0.05
Cys	59	A	.	.	.	.	T	.	-2.32	1.07	.	.	.	-0.20	0.09
Cys	60	A	.	.	.	.	T	.	-2.59	1.03	.	.	.	-0.20	0.08
Leu	61	.	.	B	B	.	.	.	-2.08	0.99	.	.	.	-0.60	0.04
Thr	62	.	.	B	B	.	.	.	-1.97	0.99	.	.	.	-0.60	0.11
Val	63	.	.	B	B	.	.	.	-1.91	1.20	.	.	.	-0.60	0.17
Val	64	.	.	B	B	.	.	.	-1.24	1.39	.	.	.	-0.60	0.33
Ser	65	.	.	B	B	.	.	.	-1.43	1.10	.	.	.	-0.60	0.40
Phe	66	A	.	.	B	.	.	.	-1.21	1.26	.	.	.	-0.60	0.40
Tyr	67	A	.	.	B	.	.	.	-1.49	1.11	.	.	.	-0.60	0.54
Gln	68	A	.	.	B	.	.	.	-1.44	0.97	.	.	.	-0.60	0.41
Val	69	A	.	.	B	.	.	.	-0.59	1.27	.	.	.	-0.60	0.39
Ala	70	A	.	.	B	.	.	.	-0.63	0.89	.	.	.	-0.60	0.43
Ala	71	A	.	.	B	.	.	.	0.07	0.56	.	*	.	-0.60	0.25
Leu	72	A	.	.	.	.	T	.	-0.50	0.16	.	*	.	0.10	0.55
Gln	73	A	.	.	.	.	T	.	-1.09	0.20	.	.	F	0.25	0.45
Gly	74	A	.	.	.	.	T	.	-0.53	0.20	.	.	F	0.25	0.45
Asp	75	A	.	.	.	.	T	.	-0.76	0.09	.	*	F	0.25	0.73
Leu	76	A	A	.	.	.	.	.	-0.06	0.09	.	*	F	-0.15	0.35
Ala	77	A	A	.	.	.	.	.	0.17	-0.31	.	*	.	0.30	0.69
Ser	78	A	A	.	.	.	.	.	0.17	-0.24	.	*	.	0.30	0.42
Leu	79	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.88
Arg	80	A	A	.	.	.	.	.	-0.30	-0.24	.	*	.	0.30	0.72
Ala	81	A	A	.	.	.	.	.	0.17	-0.34	.	*	.	0.30	0.93
Glu	82	A	A	.	.	.	.	.	0.72	-0.30	.	*	.	0.45	1.11
Leu	83	A	A	.	.	.	.	.	0.99	-0.49	.	*	.	0.30	0.77
Gln	84	A	A	.	.	.	.	.	1.21	0.01	.	*	.	-0.15	1.04
Gly	85	A	A	.	.	.	.	.	1.10	0.01	*	*	.	-0.30	0.61
His	86	A	A	.	.	.	.	.	1.73	0.01	*	*	.	-0.15	1.27
His	87	A	A	.	.	.	.	.	0.92	-0.67	.	*	.	0.75	1.47
Ala	88	A	A	.	.	.	.	.	1.52	-0.39	.	*	.	0.45	1.22
Glu	89	A	A	.	.	.	.	.	0.93	-0.39	.	.	.	0.45	1.39
Lys	90	A	A	.	.	.	.	.	0.93	-0.39	*	.	F	0.60	1.03
Leu	91	A	.	.	.	.	T	.	0.38	-0.46	*	.	.	0.85	1.01
Pro	92	A	.	.	.	.	T	.	0.07	-0.46	.	.	.	0.70	0.59
Ala	93	A	.	.	.	.	T	.	0.07	-0.03	.	.	.	0.70	0.29
Gly	94	A	.	.	.	.	T	.	-0.14	0.47	.	.	.	-0.20	0.36
Ala	95	A	.	.	.	.	.	.	-0.14	0.21	.	*	.	-0.10	0.36
Gly	96	A	.	.	.	.	.	.	0.08	-0.21	.	.	F	0.65	0.71
Ala	97	A	.	.	.	.	.	.	-0.06	-0.21	.	.	F	0.65	0.72
Pro	98	A	.	.	.	.	.	.	-0.28	-0.21	.	*	F	0.65	0.71
Lys	99	A	A	.	.	.	.	.	0.07	-0.03	.	.	F	0.45	0.59
Ala	100	A	A	.	.	.	.	.	0.66	-0.46	.	.	F	0.60	1.01

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Gly	101	A	A	.	.	.	.	.	0.41	-0.96	.	.	F	0.90	1.13
Leu	102	A	A	.	.	.	.	.	0.79	-0.89	.	.	F	0.75	0.57
Glu	103	A	A	.	.	.	.	.	0.41	-0.46	*	.	F	0.45	0.88
Glu	104	A	A	.	.	.	.	.	-0.49	-0.46	*	.	F	0.45	0.89
Ala	105	A	A	.	.	.	.	.	-0.21	-0.24	.	.	.	0.30	0.81
Pro	106	A	A	.	.	.	.	.	-0.46	-0.44	.	.	.	0.30	0.67
Ala	107	A	A	.	.	.	.	.	0.01	0.06	.	.	.	-0.30	0.39
Val	108	A	A	.	.	.	.	.	-0.80	0.49	.	*	.	-0.60	0.38
Thr	109	A	A	.	.	.	.	.	-0.76	0.67	.	*	.	-0.60	0.20
Ala	110	A	A	.	.	.	.	.	-1.06	0.24	*	*	.	-0.30	0.40
Gly	111	A	A	.	.	.	.	.	-1.54	0.43	*	*	.	-0.60	0.38
Leu	112	A	A	.	.	.	.	.	-0.96	0.57	*	*	.	-0.60	0.23
Lys	113	.	A	B	.	.	.	.	-0.31	0.09	*	*	.	-0.30	0.39
Ile	114	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	-0.30	0.61
Phe	115	.	A	B	.	.	.	.	-0.21	0.01	*	.	.	0.15	1.15
Glu	116	.	A	.	.	.	.	C	-0.08	-0.17	*	.	F	1.25	0.58
Pro	117	.	A	.	.	.	.	C	0.39	0.26	*	*	F	1.10	1.28
Pro	118	.	.	.	.	.	.	C	0.34	-0.00	.	.	F	2.20	1.47
Ala	119	.	.	.	.	.	T	C	0.89	-0.79	.	*	F	3.00	1.47
Pro	120	.	.	.	.	.	T	C	1.59	-0.36	.	*	F	2.25	0.94
Gly	121	.	.	.	.	T	T	.	1.29	-0.39	.	*	F	2.15	0.98
Glu	122	.	.	.	.	T	T	.	1.20	-0.43	.	.	F	2.00	1.30
Gly	123	.	.	.	.	.	.	C	1.41	-0.54	.	.	F	1.60	1.12
Asn	124	.	.	.	.	.	T	C	2.00	-0.57	.	.	F	1.50	1.97
Ser	125	.	.	.	.	.	T	C	1.91	-0.60	.	*	F	1.50	1.82
Ser	126	.	.	.	.	.	T	C	2.37	-0.21	.	*	F	1.54	2.47
Gln	127	.	.	.	.	.	T	C	2.37	-0.64	.	*	F	2.18	3.01
Asn	128	.	.	.	.	.	.	C	2.76	-0.64	.	.	F	2.32	3.61
Ser	129	.	.	.	.	.	T	C	2.87	-1.03	.	.	F	2.86	5.39
Arg	130	.	.	.	.	T	T	.	2.58	-1.41	*	.	F	3.40	6.09
Asn	131	.	.	.	.	T	T	.	2.02	-1.31	*	.	F	3.06	3.83
Lys	132	.	.	.	.	T	T	.	2.02	-1.07	*	.	F	2.72	2.12
Arg	133	.	.	.	.	T	.	.	1.68	-1.06	*	.	F	2.18	1.88
Ala	134	.	.	.	.	.	.	C	1.77	-0.63	*	.	F	1.64	1.15
Val	135	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.49	0.89
Gln	136	.	.	.	.	.	.	C	1.66	-0.60	*	.	F	1.83	0.79
Gly	137	.	.	.	.	.	T	C	1.30	-0.60	*	.	F	2.52	1.35
Pro	138	.	.	.	.	.	T	C	0.33	-0.61	*	.	F	2.86	2.63
Glu	139	.	.	.	.	T	T	.	0.61	-0.61	*	.	F	3.40	1.13
Glu	140	A	.	.	.	.	T	.	1.47	-0.53	*	.	F	2.66	1.64
Thr	141	A	.	.	.	.	.	.	1.47	-0.56	.	.	F	2.12	1.84
Val	142	A	.	.	.	.	.	.	1.14	-0.99	.	.	F	1.78	1.77
Thr	143	A	.	.	.	.	T	.	0.54	-0.41	.	.	F	1.19	0.55
Gln	144	A	.	.	.	.	T	.	0.54	0.27	*	.	F	0.25	0.31
Asp	145	A	.	.	.	.	T	.	-0.27	0.19	*	.	F	0.25	0.73
Cys	146	A	.	.	.	.	T	.	-0.84	0.23	*	.	.	0.10	0.42
Leu	147	A	A	.	.	.	.	.	-0.58	0.43	*	.	.	-0.60	0.17
Gln	148	A	A	.	.	.	.	.	-0.27	0.53	*	.	.	-0.60	0.10
Leu	149	A	A	.	.	.	.	.	-0.57	0.53	*	*	.	-0.30	0.32
Ile	150	A	A	.	.	.	.	.	-0.57	0.34	*	.	.	0.30	0.52

Table 9 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ala	151	.	A	.	.	.	.	C	-0.21	-0.34	.	*	.	1.40	0.52
Asp	152	.	.	.	.	T	T	.	0.39	-0.26	.	*	F	2.45	0.91
Ser	153	.	.	.	.	.	T	C	0.08	-0.51	.	.	F	3.00	2.00
Glu	154	.	.	.	.	.	T	C	-0.00	-0.71	.	.	F	2.70	2.86
Thr	155	.	.	.	.	.	T	C	0.89	-0.53	*	.	F	2.40	1.20
Pro	156	.	.	.	B	.	.	C	1.52	-0.13	*	.	F	1.56	1.55
Thr	157	.	.	.	B	T	.	.	1.18	-0.51	*	.	F	1.92	1.79
Ile	158	A	.	.	B	.	.	.	1.18	-0.09	.	.	F	1.08	1.23
Gln	159	.	.	.	.	T	T	.	0.93	-0.19	.	.	F	2.04	1.07
Lys	160	.	.	.	.	T	T	.	0.93	0.14	*	.	F	1.60	1.16
Gly	161	.	.	.	.	T	T	.	0.44	0.14	*	.	F	1.44	2.38
Ser	162	.	.	.	.	T	T	.	-0.10	0.24	*	.	F	1.28	1.19
Tyr	163	.	.	.	B	T	.	.	0.58	0.49	*	.	.	0.12	0.44
Thr	164	.	.	B	B	.	.	.	0.29	0.91	*	.	.	-0.44	0.69
Phe	165	.	.	B	B	.	.	.	-0.57	1.40	*	.	.	-0.60	0.54
Val	166	.	.	B	B	.	.	.	-1.03	1.70	.	.	.	-0.60	0.29
Pro	167	.	.	B	B	.	.	.	-1.03	1.63	.	.	.	-0.60	0.16
Trp	168	A	.	.	B	.	.	.	-1.49	1.53	.	*	.	-0.60	0.25
Leu	169	A	.	.	B	.	.	.	-1.13	1.53	*	.	.	-0.60	0.29
Leu	170	A	.	.	B	.	.	.	-0.32	0.89	*	.	.	-0.30	0.38
Ter	171	A	.	.	.	.	.	.	0.19	0.46	*	.	.	0.20	0.71
Phe	172	.	.	.	.	T	.	.	0.10	-0.03	*	.	.	1.80	0.85
Lys	173	.	.	.	.	T	T	.	-0.20	-0.33	*	.	F	2.60	1.38
Arg	174	.	.	.	.	.	T	C	-0.20	-0.51	.	.	F	3.00	1.04
Gly	175	.	.	.	.	.	T	C	0.61	-0.21	.	.	F	2.25	0.99
Ser	176	A	.	.	.	.	T	.	0.91	-1.00	*	.	F	2.05	0.86
Ala	177	A	A	.	.	.	.	.	1.66	-1.00	*	.	F	1.35	0.76
Leu	178	A	A	.	.	.	.	.	1.61	-1.00	.	.	F	1.20	1.54
Glu	179	A	A	.	.	.	.	.	1.50	-1.43	.	.	F	0.90	1.98
Glu	180	A	A	.	.	.	.	.	1.89	-1.41	*	.	F	0.90	3.16
Lys	181	A	A	.	.	.	.	.	1.30	-1.91	*	.	F	0.90	7.66
Glu	182	A	A	.	.	.	.	.	1.08	-1.91	.	.	F	0.90	3.10
Asn	183	A	A	.	.	.	.	.	1.03	-1.23	*	*	F	0.90	1.48
Lys	184	A	A	.	.	.	.	.	1.08	-0.59	*	.	F	0.75	0.55
Ile	185	A	A	.	.	.	.	.	1.08	-0.59	*	*	.	0.60	0.63
Leu	186	A	A	.	.	.	.	.	0.72	-0.59	*	*	.	0.60	0.68
Val	187	A	A	.	.	.	.	.	0.38	-0.50	.	*	.	0.30	0.49
Lys	188	A	A	.	.	.	.	.	0.13	-0.07	*	*	F	0.45	0.69
Glu	189	A	.	.	.	.	T	.	-0.61	0.00	*	*	F	0.40	1.32
Thr	190	.	.	.	.	T	T	.	-0.42	0.10	.	*	F	0.80	1.54
Gly	191	.	.	.	.	T	T	.	-0.50	0.24	*	.	F	0.65	0.67
Tyr	192	.	.	.	.	T	T	.	0.11	0.93	*	*	.	0.20	0.27
Phe	193	.	.	B	B	.	.	.	-0.28	1.69	.	.	.	-0.60	0.29
Phe	194	.	.	B	B	.	.	.	-0.28	1.63	.	*	.	-0.60	0.29
Ile	195	.	.	B	B	.	.	.	-0.82	1.60	.	.	.	-0.60	0.32
Tyr	196	.	.	B	B	.	.	.	-1.29	1.49	.	.	.	-0.60	0.28
Gly	197	.	.	.	B	T	.	.	-1.29	1.39	.	.	.	-0.20	0.26
Gln	198	.	.	.	B	T	.	.	-0.90	1.36	.	.	.	-0.20	0.59
Val	199	.	.	.	B	.	.	C	-0.20	1.16	.	.	.	-0.40	0.54
Leu	200	.	.	.	B	.	.	C	0.73	0.40	.	.	.	-0.10	0.92

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<400> 2784
Glu Arg His Tyr Tyr Asp Ile Leu Thr Gly Tyr Gln Thr Gly Tyr Gly
1 5 10 15

Met Asp Val

<210> 2785
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2785
Arg Ser Met Ile Val Val Thr Thr Ala Pro Tyr Asp Ala Phe Asp Leu
1 5 10 15

<210> 2786
<211> 15
<212> PRT
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<400> 2786
Met Asn Tyr Asp Ile Leu Thr Gly Leu Val Asn Trp Phe Asp Pro
1 5 10 15

<210> 2787
<211> 17
<212> PRT
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<400> 2787
Gly Gly Glu Leu Val Trp Phe Gly Glu Ser Asp Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 2788
<211> 13
<212> PRT
<213> Homo sapiens

<400> 2788
Thr Tyr Tyr Asp Ile Leu Thr Gly Tyr His Phe Asp Tyr
1 5 10

<210> 2789
<211> 20
<212> PRT
<213> Homo sapiens

<400> 2789
Gly Leu Arg His Val Thr Leu Phe Gly Thr Gly Thr Arg Gly His Phe
1 5 10 15

Tyr Met Asp Val
20

<210> 2790
<211> 17
<212> PRT
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<400> 2790
Gly Leu Tyr Phe Glu Asp Thr Asn Tyr Arg His Gly Asp Ala Phe Asp
1 5 10 15

Ile

<210> 2791
<211> 16
<212> PRT
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<400> 2791
Val Tyr Tyr Asp Ile Leu Thr Gly His Pro Thr Tyr Gly Met Asp Val
1 5 10 15

<210> 2792
<211> 16
<212> PRT
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<400> 2792
Gly Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile Pro Leu Arg Asp Tyr
1 5 10 15

<210> 2793
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2793
Gly Pro Trp Tyr Asp Pro Leu Phe Pro Pro Ser Gly Arg His Tyr Gly
1 5 10 15

Leu Asp Val

<210> 2794
<211> 14

<212> PRT
<213> Homo sapiens

<400> 2794
Asp Ile Asp Ala Arg Leu Ala Ala Leu Asp Ala Phe Asp Ile
1 5 10

<210> 2795
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2795
Asp Val Ser Gly His Asp Ile Leu Thr Gly Tyr Ser Tyr Arg Tyr Phe
1 5 10 15

Asp Val

<210> 2796
<211> 14
<212> PRT
<213> Homo sapiens

<400> 2796
Gly Gly His Thr Cys Ile Ile Pro Thr Cys His Met Gly Gly
1 5 10

<210> 2797
<211> 14
<212> PRT
<213> Homo sapiens

<400> 2797
Ser Gly Glu Pro Cys Ile Thr Leu Ala Cys Asn Leu Gly Gly
1 5 10

<210> 2798
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2798
Glu Arg Pro Tyr Tyr Asp Ile Leu Thr Gly Tyr Thr Val Thr Tyr Gly
1 5 10 15

Met Asp Val

<210> 2799
<211> 16
<212> PRT

<213> Homo sapiens

<400> 2799
Leu Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Pro Ser Gly Phe Asp Tyr
1 5 10 15

<210> 2800
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2800
Gly Thr Gly Tyr Asp Ile Leu Thr Gly Tyr Tyr Met Gly Ser Ala Phe
1 5 10 15

Asp Gln

<210> 2801
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2801
Gly Pro Arg Tyr Tyr Asp Ile Leu Thr Gly Tyr Arg Tyr Asn Trp Phe
1 5 10 15

Asp Pro

<210> 2802
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2802
Glu Arg Ala Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Phe Tyr Gly Met
1 5 10 15

Asp Val

<210> 2803
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2803
Asp Asp Tyr Asp Ile Leu Thr Gly Ser Leu Tyr Tyr Phe Asp Ser
1 5 10 15

<210> 2804
<211> 10
<212> PRT
<213> Homo sapiens

<400> 2804
Asp Thr Val Arg Ser Gly Gly Met Asp Val
1 5 10

<210> 2805
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2805
Val Gly Leu Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Pro Ser Gly Met
1 5 10 15

Asp Val

<210> 2806
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2806
Pro Tyr Tyr Asp Pro Leu Thr Ala Tyr Thr Phe Gln Tyr Phe Gly Asn
1 5 10 15

<210> 2807
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2807
Gly Arg Glu Asp Thr Asp Lys Val Lys Leu Trp Asp Arg Tyr Tyr His
1 5 10 15

Tyr Tyr Tyr Met Asp Val
20

<210> 2808
<211> 20
<212> PRT
<213> Homo sapiens

<400> 2808
Lys Gln Arg Gly Asp Tyr Asp Ile Leu Thr Gly Tyr Gln Leu Gly Tyr
1 5 10 15

Ala Phe Asp Ile

20

<210> 2809
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2809
Gly Arg Glu Asp Thr Asp Lys Val Lys Pro Trp Asp Arg Tyr Tyr His
1 5 10 15

Tyr Tyr Tyr Met Asp Val
20

<210> 2810
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2810
Ile Arg Leu Tyr Cys Tyr Ser Leu Thr Gly Tyr Tyr Pro Tyr Gly Met
1 5 10 15

Asp Asp

<210> 2811
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2811
Gly Arg Arg Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr His His Gly
1 5 10 15

Met Asp Val

<210> 2812
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2812
Ser Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Trp Val Pro Ala Val
1 5 10 15

<210> 2813
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2813
Gly Arg Lys Asp Thr Asp Lys Val Lys Pro Trp Asp Arg Tyr Tyr His
1 5 10 15

Tyr Tyr Tyr Met Asp Val
20

<210> 2814
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2814
Thr Asp Arg Phe Gly Ala Lys Asp Val Thr Ser Arg Trp Gly Met Asp
1 5 10 15

Val

<210> 2815
<211> 14
<212> PRT
<213> Homo sapiens

<400> 2815
Glu Gly Ala Ala Asp Tyr Leu Asn Gly Gln Tyr Phe Gln His
1 5 10

<210> 2816
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2816
Ser Ser Pro Pro Lys Trp Tyr Asp Ala Leu Thr Gly Asp Ser Ser Tyr
1 5 10 15

His Ser Ala Met Gly Val
20

<210> 2817
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2817
Val Ser Arg Asp Ile Leu Thr Gly Asn Tyr Tyr Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 2818
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2818
Ser Ser Pro Pro Lys Trp Tyr Asp Ala Leu Thr Gly Asp Ser Ser Tyr
1 5 10 15

Arg Ser Ala Met Asp Val
20

<210> 2819
<211> 20
<212> PRT
<213> Homo sapiens

<400> 2819
Val Asn Ala Asp Tyr Asp Ile Leu Thr Gly Tyr Pro Arg Asp Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> 2820
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2820
Val Arg Pro Lys Leu Arg Tyr Phe Asp Trp Leu Ser Arg His Asp Ala
1 5 10 15

Phe Asp Leu

<210> 2821
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2821
Gly Tyr Asp Asp Ile Leu Thr Gly Tyr Ile Met Ala Leu Asp Tyr
1 5 10 15

<210> 2822
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2822
Glu Ser Thr Tyr Asp Ile Leu Thr Gly Ser Tyr His Asp Tyr Gly Leu
1 5 10 15

Asp Val

<210> 2823
<211> 12
<212> PRT
<213> Homo sapiens

<400> 2823
Asp Met Lys Val Tyr Tyr Lys Tyr Ala Leu Asp Val
1 5 10

<210> 2824
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2824
Gly Gly Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile Gly Ala Phe Asp
1 5 10 15

Ile

<210> 2825
<211> 12
<212> PRT
<213> Homo sapiens

<400> 2825
Ala Gly Ser Ser Leu Val Thr Tyr Gly Thr Asp Val
1 5 10

<210> 2826
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2826
Asp Pro Phe Gly Ala Val Pro Gly Tyr Tyr Tyr Tyr Ala Met Asp Val
1 5 10 15

<210> 2827
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2827
Val Pro Tyr Asp Ile Leu Thr Gly Tyr Trp Gly Ala Phe Asp Val
1 5 10 15

<210> 2828
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2828
Asp Gln Gln Tyr Asp Ile Leu Thr Gly Tyr His Ile Asp Tyr Tyr Met
1 5 10 15

Asp Val

<210> 2829
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2829
Asp Tyr Tyr Asp Val Leu Thr Gly Phe Ser Leu Asp Gly Met Asp Val
1 5 10 15

<210> 2830
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2830
Gly Arg Asn Tyr Tyr Asp Phe Leu Thr Gly Tyr Asn Phe Asn Leu Gly
1 5 10 15

Leu Asp Tyr

<210> 2831
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2831
Met Gly His Tyr Asp Ile Leu Thr Gly Tyr Arg His Tyr Gly Met Asp
1 5 10 15

Val

<210> 2832
<211> 16

<212> PRT
<213> Homo sapiens

<400> 2832
Val Leu Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 2833
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2833
Glu Arg Ala Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Phe Tyr Asp Met
1 5 10 15

Asp Val

<210> 2834
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2834
Glu Gln Gly Tyr Asp Ile Leu Thr Gly Tyr Tyr Pro Glu Gly Gly Trp
1 5 10 15

Phe Asp Pro

<210> 2835
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2835
Gly Arg Glu Asp Thr Asp Lys Val Lys Pro Trp Asp Arg Tyr Phe His
1 5 10 15

Tyr Tyr Tyr Met Asp Val
20

<210> 2836
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2836
Glu Ser Gly Gly Tyr Ser Tyr Gly Ser Arg Asp Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> 2837
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2837
Asp Arg Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Arg Gly His Gly
1 5 10 15

Met Asp Val

<210> 2838
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2838
Glu Leu Gly His Arg Glu Gly Gly Tyr Trp Tyr Ser Pro Tyr Asn Val
1 5 10 15

<210> 2839
<211> 11
<212> PRT
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<400> 2839
Gln Gln Trp Leu Pro Tyr Asp Ala Phe Asp Ile
1 5 10

<210> 2840
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2840
Ser Asn Pro Pro Lys Trp Tyr Asp Ala Leu Thr Gly His Ser Ser Tyr
1 5 10 15

His Ser Ala Met Asp Val
20

<210> 2841
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2841

Glu Tyr Tyr Asp Val Leu Thr Gly Leu Phe Tyr Tyr Met Asp Val
1 5 10 15

<210> 2842
<211> 8
<212> PRT
<213> Homo sapiens

<400> 2842
Ser Gln Arg Leu Phe Ile Asp Ser
1 5

<210> 2843
<211> 20
<212> PRT
<213> Homo sapiens

<400> 2843
Asp Pro Ser Pro Tyr Tyr Asp Ile Leu Thr Gly Tyr Phe Leu Pro Tyr
1 5 10 15

Tyr Met Asp Val
20

<210> 2844
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2844
Gly His Tyr Asp Ile Leu Thr Gly Tyr Asp Asp Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 2845
<211> 24
<212> PRT
<213> Homo sapiens

<400> 2845
Asp Gln Asn His Pro Ile Tyr Asp Ile Leu Thr Gly Tyr Tyr Val Pro
1 5 10 15

Thr Gly Pro Leu Glu Leu Lys Asn
20

<210> 2846
<211> 18
<212> PRT

<213> Homo sapiens

<400> 2846
Gly Ile Gly Tyr Asp Leu Leu Thr Gly Tyr Phe Thr Gly Ser Pro Leu
1 5 10 15

Asp Tyr

<210> 2847
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2847
Asp Ser Gly Gly Asp Ile Leu Thr Gly Tyr Tyr Met Pro Tyr Phe Asp
1 5 10 15

Tyr

<210> 2848
<211> 22
<212> PRT
<213> Homo sapiens

<400> 2848
Ser Gly Pro Pro Lys Trp Tyr Asp Ala Leu Thr Gly His Ser Ser Tyr
1 5 10 15

His Ser Ala Met Asp Val
20

<210> 2849
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2849
Val Ser Pro Ser Tyr Asp Ile Leu Thr Gly Tyr Tyr Leu Pro His Ala
1 5 10 15

Phe Asp Val

<210> 2850
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2850

Pro Ser Tyr Asp Ile Leu Thr Gly Tyr Leu Tyr Tyr Phe Asp Tyr
1 5 10 15

<210> 2851
<211> 19
<212> PRT
<213> Homo sapiens

<400> 2851
Gly Tyr Glu Tyr Tyr Asp Ile Leu Thr Gly Tyr Asn Glu Leu Gly Ala
1 5 10 15

Phe Asp Ile

<210> 2852
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2852
Glu Leu Gly Ser Ser Ile Val Gly Ala Thr Thr Gly Ala Leu Asp Met
1 5 10 15

<210> 2853
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2853
Ser Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr His Thr Pro Leu Asp Tyr
1 5 10 15

<210> 2854
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2854
Gly Asp Tyr Asp Ile Leu Thr Gly Tyr Pro Ala Glu Cys Phe Gln Ile
1 5 10 15

<210> 2855
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2855
Ala Ser Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Lys Gly Ala Phe Asp
1 5 10 15

Ile

<210> 2856
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2856
Thr Lys Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr Tyr Met Asp Val
1 5 10 15

<210> 2857
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2857
Gly Gln Tyr Tyr Asp Ile Leu Thr Gly Tyr Asn Trp Phe Asp Pro
1 5 10 15

<210> 2858
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2858
Gly Arg Tyr Tyr Asp Met Leu Thr Arg Gly Gly Tyr Phe Asp Tyr
1 5 10 15

<210> 2859
<211> 15
<212> PRT
<213> Homo sapiens

<400> 2859
Gly Asp Tyr Asp Ile Leu Thr Gly Thr Tyr Tyr Tyr Ile Asp Val
1 5 10 15

<210> 2860
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2860
Gly Ala Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Pro Tyr Gly Met Asp
1 5 10 15

Val

<210> 2861
<211> 21

<212> PRT
<213> Homo sapiens

<400> 2861
Asp Phe Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile Gly Ala Phe
1 5 10 15

Tyr Ala Phe Asp Ile
20

<210> 2862
<211> 17
<212> PRT
<213> Homo sapiens

<400> 2862
Glu Met Gly Tyr Asp Ile Leu Thr Gly Tyr Tyr Leu Asn Tyr Met Asp
1 5 10 15

Val

<210> 2863
<211> 16
<212> PRT
<213> Homo sapiens

<400> 2863
Thr His Tyr Asp Ile Leu Thr Gly Tyr Tyr Ser His Pro Leu Asp Tyr
1 5 10 15

<210> 2864
<211> 11
<212> PRT
<213> Homo sapiens

<400> 2864
Ser Gln Trp Leu Glu His Asp Val Phe Asp Ile
1 5 10

<210> 2865
<211> 21
<212> PRT
<213> Homo sapiens

<400> 2865
Gly Gly Gly Tyr Asp Ile Leu Thr Gly Tyr Ser Tyr Pro Tyr Leu Tyr
1 5 10 15

Tyr Gly Leu Asp Val
20

Table 10 (continued)

Res	Position	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Ile	251	A	.	.	.	.	.	.	0.57	0.06	*	*	.	0.15	0.52
Ser	252	.	.	.	.	.	.	C	0.57	0.09	.	*	.	0.60	0.51
Leu	253	.	.	.	.	.	.	C	-0.29	-0.41	.	*	F	1.60	0.49
Asp	254	.	.	.	.	T	T	.	-0.01	-0.17	.	*	F	2.25	0.52
Gly	255	.	.	.	.	T	T	.	-0.71	-0.37	.	*	F	2.50	0.56
Asp	256	.	.	.	.	T	T	.	-0.52	0.03	.	*	F	1.65	0.59
Val	257	A	.	.	.	.	T	.	-0.57	0.13	.	*	F	1.00	0.30
Thr	258	A	.	.	B	.	.	.	-0.34	0.56	.	*	.	-0.10	0.30
Phe	259	A	.	.	B	.	.	.	-1.16	0.63	.	*	.	-0.35	0.18
Phe	260	A	.	.	B	.	.	.	-0.77	1.31	.	*	.	-0.60	0.20
Gly	261	A	A	.	.	.	.	.	-1.58	0.67	.	*	.	-0.60	0.28
Ala	262	A	A	.	.	.	.	.	-1.53	0.87	.	*	.	-0.60	0.27
Leu	263	A	A	.	.	.	.	.	-1.61	0.77	*	.	.	-0.60	0.26
Lys	264	A	A	.	.	.	.	.	-1.30	0.41	*	.	.	-0.60	0.33
Leu	265	A	A	.	.	.	.	.	-0.99	0.41	.	.	.	-0.60	0.42
Leu	266	A	A	.	.	.	.	.	-1.03	0.34	*	.	.	-0.30	0.65

[083] In another embodiment, the invention provides antibodies that bind a polypeptide comprising, or alternatively consisting of, an epitope-bearing portion of a polypeptide of the invention. The epitope of this polypeptide portion may be an immunogenic or antigenic epitope of a polypeptide of the invention. An "immunogenic epitope" is defined as a part of a protein that elicits an antibody response when the whole protein is the immunogen. On the other hand, a region of a protein molecule to which an antibody can bind is defined as an "antigenic epitope." The number of immunogenic epitopes of a protein generally is less than the number of antigenic epitopes. See, for instance, Geysen *et al., Proc. Natl. Acad. Sci. USA 81*:3998- 4002 (1983).

[084] As to the selection of polypeptides bearing an antigenic epitope (i.e., that contain a region of a protein molecule to which an antibody can bind), it is well known in that art that relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for instance, Sutcliffe, J. G., Shinnick, T. M., Green, N. and Learner, R. A. (1983) "Antibodies that react with predetermined sites on proteins", *Science, 219*:660-666. Peptides capable of eliciting protein-reactive sera are frequently represented in the primary sequence of a protein, can be characterized by a set of simple chemical rules, and are confined neither to immunodominant regions of intact proteins (i.e., immunogenic epitopes) nor to the amino or carboxyl terminals. Antigenic epitope-bearing peptides and polypeptides of the invention are therefore useful to raise antibodies, including monoclonal antibodies, that bind specifically to a polypeptide of the invention. See, for instance, Wilson *et al., Cell 37*:767-778 (1984) at 777.

[085] In specific embodiments, antibodies of the present invention bind antigenic epitope-bearing peptides and polypeptides of BLyS and preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids contained within the amino acid sequence of a BLyS polypeptide. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof.

[086] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLyS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-115 to about Leu-147 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-150 to about Tyr-163 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-171 to about Phe-194 in SEQ ID NO:3228; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-223 to about Tyr-246 in SEQ ID NO:3228; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-271 to about Phe-278 in Figures 1A and 1B (SEQ ID NO:3228). In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLyS polypeptide by the analysis of the Jameson-Wolf antigenic index, as disclosed Table 9, above.

[087] Non-limiting examples of antigenic polypeptides or peptides that can be used to generate BLyS-specific antibodies and which may be bound by the antibodies of the invention include: a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-32 to about Leu-47 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Glu-116 to about Ser-143 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Phe-153 to about Tyr-173 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Pro-218 to about Tyr-227 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ala-232 to about Gln-241 in SEQ ID NO:3229; a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ile-244 to about Ala-249 in SEQ ID NO:3229; and a polypeptide comprising, or alternatively consisting of, amino acid residues from about Ser-252 to about Val-257 in SEQ ID NO:3229. In this context, "about" means the particularly recited ranges and ranges larger or smaller by several, a few, 5, 4, 3, 2 or 1 amino acid residues at either or both the amino- and carboxy-termini. These polypeptide fragments have been determined to bear antigenic epitopes of the BLyS polypeptide by the analysis of the Jameson-Wolf

antigenic index, as disclosed in Table 10 generated by the Protean component of the DNA*STAR computer program (as set forth above).

[088] BLyS epitope-bearing peptides and polypeptides may be produced by any conventional means. *See, e.g.*, Houghten, R. A. (1985) General method for the rapid solid-phase synthesis of large numbers of peptides: specificity of antigen-antibody interaction at the level of individual amino acids. *Proc. Natl. Acad. Sci. USA 82*:5131-5135; this "Simultaneous Multiple Peptide Synthesis (SMPS)" process is further described in U. S. Patent No. 4,631,211 to Houghten et al. (1986).

[089] The present invention encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3228, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 97768, or encoded by a polynucleotide that hybridizes to cDNA sequence contained in ATCC deposit No. 97768 (e.g., under hybridization conditions described herein).

[090] The present invention also encompasses antibodies that bind polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:3229, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. 203518, or encoded by a polynucleotide that hybridizes to the cDNA sequence contained in ATCC deposit No. 203518 (e.g., under hybridization conditions described herein).

[091] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses antibodies that bind a polypeptide comprising an epitope. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not

necessarily be immunogenic.

[092] BLyS polypeptide fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

[093] In the present invention, antibodies of the present invention bind antigenic epitopes preferably containing a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes that may be bound by antibodies of the present invention are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[094] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes of BLyS may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[095] Epitope-bearing BLyS polypeptides may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemocyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl-N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier-coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 micrograms of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[096] As one of skill in the art will appreciate, and as discussed above, the antibodies of the present invention may bind polypeptides comprising an immunogenic or antigenic epitope fused to other polypeptide sequences. For example, the BLyS polypeptides may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof), or albumin (including but not limited to recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of

mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, Proc. Natl. Acad. Sci. USA 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix-binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni^{2+} nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

[097] In another embodiment, the antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with a heterologous antigen (e.g., polypeptide, carbohydrate, phospholipid, or nucleic acid). In specific embodiments, the heterologous antigen is an immunogen.

[098] In a more specific embodiment, the heterologous antigen is the gp120 protein of HIV, or a fragment thereof.

[099] In another embodiment, antibodies of the present invention bind BLyS polypeptides and/or the epitope-bearing fragments thereof that are fused with polypeptide sequences of another TNF ligand family member (or biologically active fragments or variants thereof). In a specific embodiment, the antibodies of the present invention bind BLyS polypeptides of the present invention are fused with a CD40L polypeptide sequence. In a preferred embodiment, the CD40L polypeptide sequence is soluble.

[0100] In another embodiment, antibodies of the present invention bind mutant

BLyS polypeptides that have been generated by random mutagenesis of a polynucleotide encoding the BLyS polypeptide, by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, antibodies of the present invention bind one or more components, motifs, sections, parts, domains, fragments, etc., of BLyS recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are, for example, TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), AIM-II (International Publication No. WO 97/34911), APRIL (J. Exp. Med. 188(6):1185-1190), endokine-alpha (International Publication No. WO 98/07880), OPG, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202),312C2 (International Publication No. WO 98/06842), TR12, CAD, and v-FLIP. In further embodiments, the heterologous molecules are any member of the TNF family.

[0101] In another preferred embodiment, antibodies of the present invention bind BLyS polypeptides of the invention (including biologically active fragments or variants thereof), that are fused with soluble APRIL polypeptides (e.g., amino acid residues 105 through 250 of SEQ ID NO:3239), or biologically active fragments or variants thereof.

[0102] To improve or alter the characteristics of BLyS polypeptides, protein engineering may be employed. Recombinant DNA technology known to those skilled in the art can be used to create novel mutant proteins or "muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than the corresponding natural polypeptide, at least under certain purification and storage conditions. For instance, for many proteins, including the extracellular domain or the mature form(s) of a secreted

protein, it is known in the art that one or more amino acids may be deleted from the N-terminus or C-terminus without substantial loss of biological function. For instance, Ron et al., J. Biol. Chem., 268:2984-2988 (1993) reported modified KGF proteins that had heparin binding activity even if 3, 8, or 27 amino-terminal amino acid residues were missing. Accordingly, antibodies of the present invention may bind BLyS polypeptide mutants or variants generated by protein engineering.

[0103] In the present case, since the protein of the invention is a member of the TNF polypeptide family, deletions of N-terminal amino acids up to the Gly (G) residue at position 191 in SEQ ID NO:3228 may retain some biological activity such as, for example, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and cytotoxicity to appropriate target cells. Polypeptides having further N-terminal deletions including the Gly (G) residue would not be expected to retain biological activities because it is known that this residue in TNF-related polypeptides is in the beginning of the conserved domain required for biological activities. However, even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities may still be retained. Thus, the ability of the shortened protein to induce and/or bind to antibodies which recognize the complete or extracellular domain of the protein generally will be retained when less than the majority of the residues of the complete or extracellular domain of the protein are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete protein retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0104] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of the BLyS of SEQ ID NO:3228, up to the glycine residue at position 191 (Gly-191 residue from the amino terminus). In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^1-285 of SEQ ID NO:3228, where n^1 is an integer in the range of the amino acid position of amino acid residues 2-190 of the amino acid sequence in SEQ ID NO:3228. More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group

consisting of residues 2-285, 3-285, 4-285, 5-285, 6-285, 7-285, 8-285, 9-285, 10-285, 11-285, 12-285, 13-285, 14-285, 15-285, 16-285, 17-285, 18-285, 19-285, 20-285, 21-285, 22-285, 23-285, 24-285, 25-285, 26-285, 27-285, 28-285, 29-285, 30-285, 31-285, 32-285, 33-285, 34-285, 35-285, 36-285, 37-285, 38-285, 39-285, 40-285, 41-285, 42-285, 43-285, 44-285, 45-285, 46-285, 47-285, 48-285, 49-285, 50-285, 51-285, 52-285, 53-285, 54-285, 55-285, 56-285, 57-285, 58-285, 59-285, 60-285, 61-285, 62-285, 63-285, 64-285, 65-285, 66-285, 67-285, 68-285, 69-285, 70-285, 71-285, 72-285, 73-285, 74-285, 75-285, 76-285, 77-285, 78-285, 79-285, 80-285, 81-285, 82-285, 83-285, 84-285, 85-285, 86-285, 87-285, 88-285, 89-285, 90-285, 91-285, 92-285, 93-285, 94-285, 95-285, 96-285, 97-285, 98-285, 99-285, 100-285, 101-285, 102-285, 103-285, 104-285, 105-285, 106-285, 107-285, 108-285, 109-285, 110-285, 111-285, 112-285, 113-285, 114-285, 115-285, 116-285, 117-285, 118-285, 119-285, 120-285, 121-285, 122-285, 123-285, 124-285, 125-285, 126-285, 127-285, 128-285, 129-285, 130-285, 131-285, 132-285, 133-285, 134-285, 135-285, 136-285, 137-285, 138-285, 139-285, 140-285, 141-285, 142-285, 143-285, 144-285, 145-285, 146-285, 147-285, 148-285, 149-285, 150-285, 151-285, 152-285, 153-285, 154-285, 155-285, 156-285, 157-285, 158-285, 159-285, 160-285, 161-285, 162-285, 163-285, 164-285, 165-285, 166-285, 167-285, 168-285, 169-285, 170-285, 171-285, 172-285, 173-285, 174-285, 175-285, 176-285, 177-285, 178-285, 179-285, 180-285, 181-285, 182-285, 183-285, 184-285, 185-285, 186-285, 187-285, 188-285, 189-285, and 190-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0105] Furthermore, since the predicted extracellular domain of the BLyS polypeptides of the invention may itself elicit biological activity, deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide (spanning positions Gln-73 to Leu-285 of SEQ ID NO:3228) may retain some biological activity such as, for example, ligand binding, stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, and modulation of cell replication or modulation of target cell activities. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results

in modification or loss of one or more biological functions of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0106] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3228, up to the glycine residue at position number 280. In particular, the present invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues n^2-285 of SEQ ID NO:3228, where n^2 is an integer in the range of the amino acid position of amino acid residues 73-280 in SEQ ID NO:3228, and 73 is the position of the first residue from the N-terminus of the predicted extracellular domain of the BLyS polypeptide (disclosed in SEQ ID NO:3228). More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-285; G-74 to L-285; D-75 to L-285; L-76 to L-285; A-77 to L-285; S-78 to L-285; L-79 to L-285; R-80 to L-285; A-81 to L-285; E-82 to L-285; L-83 to L-285; Q-84 to L-285; G-85 to L-285; H-86 to L-285; H-87 to L-285; A-88 to L-285; E-89 to L-285; K-90 to L-285; L-91 to L-285; P-92 to L-285; A-93 to L-285; G-94 to L-285; A-95 to L-285; G-96 to L-285; A-97 to L-285; P-98 to L-285; K-99 to L-285; A-100 to L-285; G-101 to L-285; L-102 to L-285; E-103 to L-285; E-104 to L-285; A-105 to L-285; P-106 to L-285; A-107 to L-285; V-108 to L-285; T-109 to L-285; A-110 to L-285; G-111 to L-285; L-112 to L-285; K-113 to L-285; I-114 to L-285; F-115 to L-285; E-116 to L-285; P-117 to L-285; P-118 to L-285; A-119 to L-285; P-120 to L-285; G-121 to L-285; E-122 to L-285; G-123 to L-285; N-124 to L-285; S-125 to L-285; S-126 to L-285; Q-127 to L-285; N-128 to L-285; S-129 to L-285; R-130 to L-285; N-131 to L-285; K-132 to L-285; R-133 to L-285; A-134 to L-285; V-135 to L-285; Q-136 to L-285; G-137 to L-285; P-138 to L-285; E-139 to L-285; E-140 to L-285; T-141 to L-285; V-142 to L-285;

T-143 to L-285; Q-144 to L-285; D-145 to L-285; C-146 to L-285; L-147 to L-285; Q-148 to L-285; L-149 to L-285; I-150 to L-285; A-151 to L-285; D-152 to L-285; S-153 to L-285; E-154 to L-285; T-155 to L-285; P-156 to L-285; T-157 to L-285; I-158 to L-285; Q-159 to L-285; K-160 to L-285; G-161 to L-285; S-162 to L-285; Y-163 to L-285; T-164 to L-285; F-165 to L-285; V-166 to L-285; P-167 to L-285; W-168 to L-285; L-169 to L-285; L-170 to L-285; S-171 to L-285; F-172 to L-285; K-173 to L-285; R-174 to L-285; G-175 to L-285; S-176 to L-285; A-177 to L-285; L-178 to L-285; E-179 to L-285; E-180 to L-285; K-181 to L-285; E-182 to L-285; N-183 to L-285; K-184 to L-285; I-185 to L-285; L-186 to L-285; V-187 to L-285; K-188 to L-285; E-189 to L-285; T-190 to L-285; G-191 to L-285; Y-192 to L-285; F-193 to L-285; F-194 to L-285; I-195 to L-285; Y-196 to L-285; G-197 to L-285; Q-198 to L-285; V-199 to L-285; L-200 to L-285; Y-201 to L-285; T-202 to L-285; D-203 to L-285; K-204 to L-285; T-205 to L-285; Y-206 to L-285; A-207 to L-285; M-208 to L-285; G-209 to L-285; H-210 to L-285; L-211 to L-285; I-212 to L-285; Q-213 to L-285; R-214 to L-285; K-215 to L-285; K-216 to L-285; V-217 to L-285; H-218 to L-285; V-219 to L-285; F-220 to L-285; G-221 to L-285; D-222 to L-285; E-223 to L-285; L-224 to L-285; S-225 to L-285; L-226 to L-285; V-227 to L-285; T-228 to L-285; L-229 to L-285; F-230 to L-285; R-231 to L-285; C-232 to L-285; I-233 to L-285; Q-234 to L-285; N-235 to L-285; M-236 to L-285; P-237 to L-285; E-238 to L-285; T-239 to L-285; L-240 to L-285; P-241 to L-285; N-242 to L-285; N-243 to L-285; S-244 to L-285; C-245 to L-285; Y-246 to L-285; S-247 to L-285; A-248 to L-285; G-249 to L-285; I-250 to L-285; A-251 to L-285; K-252 to L-285; L-253 to L-285; E-254 to L-285; E-255 to L-285; G-256 to L-285; D-257 to L-285; E-258 to L-285; L-259 to L-285; Q-260 to L-285; L-261 to L-285; A-262 to L-285; I-263 to L-285; P-264 to L-285; R-265 to L-285; E-266 to L-285; N-267 to L-285; A-268 to L-285; Q-269 to L-285; I-270 to L-285; S-271 to L-285; L-272 to L-285; D-273 to L-285; G-274 to L-285; D-275 to L-285; V-276 to L-285; T-277 to L-285; F-278 to L-285; F-279 to L-285; and G-280 to L-285 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0107] Highly preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an

amino acid sequence least 80%, 85%, 90% identical and more preferably at least 95%, 96%, 97%, 98%, 99% or 100% identical to BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0108] Preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 90% identical to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 95% identical to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. More preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 96% identical to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0109] Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 97% to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 98% to a BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228. Additionally, more preferred embodiments of the invention are directed to antibodies that bind polypeptides comprising, or alternatively consisting of, a polypeptide having an amino acid sequence at least 99% identical to BLyS polypeptide having the amino acid sequence at positions 134-285 of SEQ ID NO:3228.

[0110] In specific embodiments, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, one of the following N-terminally deleted polypeptide fragments of BLyS: amino acid residues Ala-71 through Leu-285, amino acid residues Ala-81 through Leu-285, amino acid residues Leu-112 through Leu-285, amino acid residues Ala-134 through Leu-285, amino acid residues Leu-147 through Leu-285, and amino acid residues Gly-161 through Leu-285 of SEQ ID NO:3228.

[0111] Similarly, many examples of biologically functional C-terminal deletion

<210> 2866
<211> 13
<212> PRT
<213> Homo sapiens

<400> 2866
Thr Tyr Tyr Asp Ile Leu Thr Gly Arg Phe Phe Asp Ile
1 5 10

<210> 2867
<211> 13
<212> PRT
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<400> 2867
Asp Val Asp Asp Ile Leu Thr Gly Tyr Ser Trp Asp Tyr
1 5 10

<210> 2868
<211> 16
<212> PRT
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<400> 2868
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1 5 10 15

<210> 2869
<211> 15
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<400> 2869
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1 5 10 15

<210> 2870
<211> 8
<212> PRT
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<400> 2870
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1 5

<210> 2871
<211> 17
<212> PRT
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<400> 2871
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Val

<210> 2872
<211> 17
<212> PRT
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1 5 10 15

Ile

<210> 2873
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<400> 2873
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<210> 2874
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Val

<210> 2875
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<400> 2875
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Gly Met Asp Val
20

<210> 2876

<211> 17
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<400> 2876
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Val

<210> 2877
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<212> PRT
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<400> 2877
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1 5 10 15

Met Asp Val

<210> 2878
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Ser

<210> 2879
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<400> 2879
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1 5 10

<210> 2880
<211> 18
<212> PRT
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1 5 10 15

Asp Met

<210> 2881
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<400> 2881
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Asp Tyr

<210> 2882
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<212> PRT
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1 5 10 15

<210> 2883
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1 5 10

<210> 2885
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Phe Asp Ile

<210> 2886
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<210> 2887
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Asp Ala Phe Asp Ile
20

<210> 2888
<211> 23
<212> PRT
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1 5 10 15

Gly Arg Asn Trp Phe Asp Pro
20

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<400> 2889
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1 5 10 15

Met Asp Val

<210> 2890
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<212> PRT
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<400> 2890
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1 5 10 15

<210> 2891
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<400> 2891
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1 5 10 15

<210> 2892
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1 5 10 15

Ile

<210> 2893
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1 5 10 15

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1 5 10 15

<210> 2895
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1 5 10 15

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<400> 2896
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Ala Phe Asp Ile
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<210> 2897
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<400> 2897
Gly Thr Gly Tyr Asp Ile Leu Thr Gly Tyr Tyr Met Gly Ser Val Phe
1 5 10 15

Asp Pro

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<400> 2898
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1 5 10 15

<210> 2899
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1 5 10 15

Met Asp Val

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1 5 10 15

Gly Met Asp Val
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<210> 2901
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Gly Ser Phe Asp Ile
20

<210> 2902
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<400> 2902
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1 5 10 15

Tyr

<210> 2903
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<400> 2903
Glu Gly Glu Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile Gly Asn Gly
1 5 10 15

Ala Phe Asp Ile
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His Asp Ile Leu Thr Gly Phe Asp Tyr

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<212> PRT
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<400> 2905
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<210> 2906
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1 5 10 15

<210> 2907
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Glu His Tyr Asp Ile Leu Thr Gly Tyr Ser Leu Leu Gly Met Asp Val
1 5 10 15

<210> 2908
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<400> 2908
Gly Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Ser His Phe Asp Tyr
1 5 10 15

<210> 2909
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<400> 2909
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1 5 10 15

<210> 2910
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1 5 10 15

<210> 2911
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<400> 2911
Ala Phe Glu Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr His His Asp Ala
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Phe Asp Ile

<210> 2912
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1 5 10 15

Tyr Tyr Gly Met Asp Val
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<210> 2913
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<400> 2913
Asp Arg Arg Asp Ile Leu Thr Gly Ser Asn Phe Gly Gln Asp
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<210> 2914
<211> 20
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<400> 2914
Asp Arg Gly Gly Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Phe His His
1 5 10 15

Gly Val Asp Val
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<210> 2915
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<213> Homo sapiens

<400> 2915
Asp Gly Thr Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Gln Tyr Gly
1 5 10 15

Met Asp Val

<210> 2916
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<212> PRT
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<400> 2916
Gly Gln Lys Asn Tyr Tyr Glu Ser Ser Gly Tyr Leu Glu His
1 5 10

<210> 2917
<211> 18
<212> PRT
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<400> 2917
Asp Met His Tyr Asp Ile Leu Thr Gly Tyr Tyr Thr Gly Leu Ala Phe
1 5 10 15

Asp Met

<210> 2918
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Asp Gln Val Asp Leu Leu Leu Met Asp His Asn Tyr Tyr Met Asp Val
1 5 10 15

<210> 2919
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<400> 2919
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1 5 10 15

<210> 2920
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<400> 2920
Arg Arg Tyr Ala Leu Asp Tyr
1 5

<210> 2921
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<400> 2921
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1 5 10 15

<210> 2922
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<400> 2922
Asp Pro Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Phe His Arg Tyr Gly
1 5 10 15

Met Asp Val

<210> 2923
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<400> 2923
Asp Leu Pro Tyr Tyr Asp Ile Leu Thr Gly Tyr Ser Leu Thr Ser Gly
1 5 10 15

Met Asp Val

<210> 2924
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<212> PRT
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<400> 2924
Asp Ile Asp Asp Ile Leu Thr Gly Tyr Val Leu Gly Met Asp Val
1 5 10 15

<210> 2925
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<400> 2925
Pro Gln Gly Val Thr Leu Val Arg Gly Ala Glu Thr Asp Ala Phe Ala
1 5 10 15

Ile

<210> 2926
<211> 24
<212> PRT
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<400> 2926
Asp Tyr Pro Gly Ser Glu Tyr Asp Ile Leu Thr Gly Tyr Leu Phe Gly
1 5 10 15

Tyr Tyr Tyr Tyr Gly Met Asp Val
20

<210> 2927
<211> 16
<212> PRT
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<400> 2927
Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Gln Ser Asp Ala Phe Asp Ile
1 5 10 15

<210> 2928
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<212> PRT
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<400> 2928
Asp Arg Arg Asp Tyr Asp Leu Leu Thr Arg Tyr Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 2929
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<400> 2929
Pro Leu Gly Ile Thr Ala Val Arg Gly Ala Lys Thr Asp Ala Phe Gly
1 5 10 15

Ile

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<400> 2930
His Arg Arg Ala Arg Val Val Val Pro Val Pro Gly Ala Met Asp Val
1 5 10 15

<210> 2931
<211> 18
<212> PRT
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<400> 2931
Asp Arg Gly Tyr Thr Gly Tyr Asp Arg Leu Val Gly Gly Tyr Tyr Phe
1 5 10 15

Asp Phe

<210> 2932
<211> 16
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<400> 2932
Thr Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Ala Glu Tyr Phe Gln His
1 5 10 15

<210> 2933
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Arg Asp Ile Leu Thr Gly Phe Tyr Asp Ser
1 5 10

<210> 2934
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<400> 2934
Ser Gly Tyr Asp Ile Leu Thr Gly Tyr Leu Tyr Gly Met Asp Val
1 5 10 15

<210> 2935
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<400> 2935
Asp Pro Gly Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 2936
<211> 19
<212> PRT
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<400> 2936
Glu Gly Thr Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Pro Leu Gly Tyr
1 5 10 15

Phe Asp Tyr

<210> 2937
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<212> PRT
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<400> 2937
Gly Val Val Trp Val Ala Tyr Gly Asp Val Gly Ile Tyr Gly Phe Asp
1 5 10 15

Val

<210> 2938
<211> 18
<212> PRT
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<400> 2938
Asp Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Ser Val Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 2939
<211> 19
<212> PRT
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<400> 2939

Val Leu Thr Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Arg Glu Asp Ala
1 5 10 15

Phe Asp Met

<210> 2940
<211> 18
<212> PRT
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<400> 2940
Thr Glu Ser Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Trp Pro Ser Met
1 5 10 15

Asp Val

<210> 2941
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<212> PRT
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<400> 2941
Gly Asp Tyr Asp Pro Leu Thr Gly Tyr Ser Phe Gly Val Asp Val
1 5 10 15

<210> 2942
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Asp Asn Tyr Asp Ile Leu Thr Gly Tyr Ser Arg Arg Phe Asp Pro
1 5 10 15

<210> 2943
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<400> 2943
Gly Gln Phe Gly Val Leu Pro Asn Tyr Tyr Tyr His Met Asp Val
1 5 10 15

<210> 2944
<211> 19
<212> PRT
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<400> 2944
Leu Gly Arg Thr Ser Arg Asp Leu Leu Thr Gly Tyr His Phe Tyr Asn

1 5 10 15

Met Asp Val

<210> 2945
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<400> 2945
Asp Arg Glu Thr Lys Val Gly Tyr Gly Met Asp Val
1 5 10

<210> 2946
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<212> PRT
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<400> 2946
Asp Met Gly Tyr Asp Ile Leu Thr Gly Tyr Tyr Gly Ala Phe Asp Ile
1 5 10 15

<210> 2947
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<212> PRT
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<400> 2947
Ala Tyr Tyr Asp Asn Leu Thr Gly Phe Leu Pro Tyr Gly Met Gly Val
1 5 10 15

<210> 2948
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<212> PRT
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<400> 2948
Gly Glu Arg Asp Ile Leu Thr Gly Tyr Tyr Leu Asp Gly Met Asp Val
1 5 10 15

<210> 2949
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Ala Thr Tyr Asp Pro Leu Thr Gly Tyr Tyr Phe Asp Gly Phe Asp Ile
1 5 10 15

<210> 2950
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<212> PRT
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<400> 2950
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1 5 10 15

<210> 2951
<211> 8
<212> PRT
<213> Homo sapiens

<400> 2951
Gly Tyr Asp Thr Ala Met Gln Tyr
1 5

<210> 2952
<211> 16
<212> PRT
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<400> 2952
Leu Asn Leu Glu Lys Thr Val Val Arg Gly Phe Gly Tyr Phe Asp Leu
1 5 10 15

<210> 2953
<211> 20
<212> PRT
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<400> 2953
Leu Lys Ala Pro Tyr Tyr Asp Leu Leu Thr Gly Tyr His Leu Pro Lys
1 5 10 15

Trp Phe Asp Thr
20

<210> 2954
<211> 9
<212> PRT
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<400> 2954
Asp Ile Asp Ile Gly Gly Asp Asp Ser
1 5

<210> 2955
<211> 17
<212> PRT
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<400> 2955
Val Ser Asn Asp Ile Leu Thr Gly Trp Gly Gly Tyr Asn Trp Phe Asp

1 5 10 15

Pro

<210> 2956
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<212> PRT
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<400> 2956
Glu Arg Ser Gln Phe Asp Phe Leu Thr Gly Val Asp Arg Tyr His Pro
1 5 10 15

Met Asp Val

<210> 2957
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<212> PRT
<213> Homo sapiens

<400> 2957
Ser Ser Asn Pro Val Tyr Gly Leu Asp Val
1 5 10

<210> 2958
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<212> PRT
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<400> 2958
Arg Gln Tyr Asp Ile Leu Thr Gly Tyr Tyr Gly Gly Phe Asp Tyr
1 5 10 15

<210> 2959
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<400> 2959
Gly Leu Gly His Thr Asp Ser Asp Ser
1 5

<210> 2960
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<400> 2960
Asp Arg Glu Tyr Asp Leu Leu Thr Gly Tyr Tyr Leu His Ala Phe Asp
1 5 10 15

Met

<210> 2961
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<400> 2961
Ala Gly Ser Gly Phe His Asp Ile Leu Thr Gly Tyr Tyr Lys Gly Gly
1 5 10 15

Tyr Phe Asp Tyr
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<210> 2962
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<400> 2962
Gly Gly Pro His Tyr Asp Ile Leu Thr Gly Tyr Tyr Met Ala Val Gly
1 5 10 15

Phe Asp Ile

<210> 2963
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<212> PRT
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<400> 2963
Asp Leu Gly Ser Phe Tyr Asp Ile Leu Thr Ala Leu Arg Leu Glu Asn
1 5 10 15

Tyr Gly Met Asp Val
20

<210> 2964
<211> 18
<212> PRT
<213> Homo sapiens

<400> 2964
Asp Gln Gln Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile His Tyr Gly Met
1 5 10 15

Asp Val

antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3228, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m^3 of SEQ ID NO:3228, where m^3 is an integer in the range of the amino acid position of amino acid residues 6-284 of the amino acid sequence in SEQ ID NO:3228.

[0124] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-284; M-1 to K-283; M-1 to L-282; M-1 to A-281; M-1 to G-280; M-1 to F-279; M-1 to F-278; M-1 to T-277; M-1 to V-276; M-1 to D-275; M-1 to G-274; M-1 to D-273; M-1 to L-272; M-1 to S-271; M-1 to I-270; M-1 to Q-269; M-1 to A-268; M-1 to N-267; M-1 to E-266; M-1 to R-265; M-1 to P-264; M-1 to I-263; M-1 to A-262; M-1 to L-261; M-1 to Q-260; M-1 to L-259; M-1 to E-258; M-1 to D-257; M-1 to G-256; M-1 to E-255; M-1 to E-254; M-1 to L-253; M-1 to K-252; M-1 to A-251; M-1 to I-250; M-1 to G-249; M-1 to A-248; M-1 to S-247; M-1 to Y-246; M-1 to C-245; M-1 to S-244; M-1 to N-243; M-1 to N-242; M-1 to P-241; M-1 to L-240; M-1 to T-239; M-1 to E-238; M-1 to P-237; M-1 to M-236; M-1 to N-235; M-1 to Q-234; M-1 to I-233; M-1 to C-232; M-1 to R-231; M-1 to F-230; M-1 to L-229; M-1 to T-228; M-1 to V-227; M-1 to L-226; M-1 to S-225; M-1 to L-224; M-1 to E-223; M-1 to D-222; M-1 to G-221; M-1 to F-220; M-1 to V-219; M-1 to H-218; M-1 to V-217; M-1 to K-216; M-1 to K-215; M-1 to R-214; M-1 to Q-213; M-1 to I-212; M-1 to L-211; M-1 to H-210; M-1 to G-209; M-1 to M-208; M-1 to A-207; M-1 to Y-206; M-1 to T-205; M-1 to K-204; M-1 to D-203; M-1 to T-202; M-1 to Y-201; M-1 to L-200; M-1 to V-199; M-1 to Q-198; M-1 to G-197; M-1 to Y-196; M-1 to I-195; M-1 to F-194; M-1 to F-193; M-1 to Y-192; M-1 to G-191; M-1 to T-190; M-1 to E-189; M-1 to K-188; M-1 to V-187; M-1 to L-186; M-1 to I-185; M-1 to K-184; M-1 to N-183; M-1 to E-182; M-1 to K-181; M-1 to E-180; M-1 to E-179; M-1 to L-178; M-1 to A-177; M-1 to S-176; M-1 to G-175; M-1 to R-174; M-1 to K-173; M-1 to F-172; M-1 to S-171; M-1 to L-170; M-1 to L-169; M-1 to W-168; M-1 to P-167; M-1 to V-166; M-1 to F-165; M-1 to T-164; M-1 to Y-163; M-1 to S-162; M-1 to G-161; M-1 to K-160; M-1 to Q-159; M-1 to I-158; M-1 to T-157; M-1 to P-156; M-1 to T-155; M-1 to E-154; M-1 to S-153; M-1 to D-152; M-1 to A-151; M-1 to I-150; M-1 to L-149; M-1 to

Q-148; M-1 to L-147; M-1 to C-146; M-1 to D-145; M-1 to Q-144; M-1 to T-143; M-1 to V-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15; M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0125] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n^3-m^3 of SEQ ID NO:3228, where n^3 and m^3 are integers as defined above.

[0126] Furthermore, since the predicted extracellular domain of the BLyS

polypeptide of SEQ ID NO:3229 may itself elicit functional activity (e.g., biological activity), deletions of N- and C-terminal amino acid residues from the predicted extracellular region of the polypeptide at positions Gln-73 to Leu-266 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, to stimulation of lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. However, even if deletion of one or more amino acids from the N-terminus of the predicted extracellular domain of a BLyS polypeptide results in modification or loss of one or more functional activities of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptides to induce and/or bind to antibodies which recognize the complete or mature or extracellular domains of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature or extracellular domains of the polypeptides are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0127] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of BLyS shown in SEQ ID NO:3229, up to the glycine residue at position number 261. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^4-266 of SEQ ID NO:3229, where n^4 is an integer in the range of the amino acid position of amino acid residues 73-261 of the amino acid sequence in SEQ ID NO:3229, and 261 is the position of the first residue from the N-terminus of the predicted extracellular domain BLyS polypeptide (shown in SEQ ID NO:3229).

[0128] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to

L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies

that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0129] Similarly, deletions of C-terminal amino acid residues of the predicted extracellular domain of BLyS up to the leucine residue at position 79 of SEQ ID NO:3229 may retain some functional activity, such as, for example, ligand binding, the ability to stimulate lymphocyte (e.g., B cell) proliferation, differentiation, and/or activation, modulation of cell replication, modulation of target cell activities and/or immunogenicity. Polypeptides having further C-terminal deletions including Leu-79 of SEQ ID NO:3229 would not be expected to retain biological activities.

[0130] However, even if deletion of one or more amino acids from the C-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete, mature or extracellular forms of the polypeptide generally will be retained when less than the majority of the residues of the complete, mature or extracellular forms of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of the predicted extracellular domain retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0131] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of the predicted extracellular domain of BLyS shown in SEQ ID NO:3229, up to the leucine residue at position 79 of SEQ ID NO:3229. In particular, the present invention provides antibodies that bind polypeptides having the amino acid sequence of residues 73-m^4 of the amino acid sequence in SEQ ID NO:3229, where m^4 is any integer in the range of the amino acid position of amino acid residues 79-265 of the amino acid sequence in SEQ ID NO:3229.

[0132] More in particular, in certain embodiments, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues Q-73 to L-265; Q-73 to K-264; Q-73 to L-263; Q-73 to A-262; Q-73 to G-261; Q-73 to F-260; Q-73 to F-259; Q-73 to

T-258; Q-73 to V-257; Q-73 to D-256; Q-73 to G-255; Q-73 to D-254; Q-73 to L-253; Q-73 to S-252; Q-73 to I-251; Q-73 to Q-250; Q-73 to A-249; Q-73 to N-248; Q-73 to E-247; Q-73 to R-246; Q-73 to P-245; Q-73 to I-244; Q-73 to A-243; Q-73 to L-242; Q-73 to Q-241; Q-73 to L-240; Q-73 to E-239; Q-73 to D-238; Q-73 to G-237; Q-73 to E-236; Q-73 to E-235; Q-73 to L-234; Q-73 to K-233; Q-73 to A-232; Q-73 to I-231; Q-73 to G-230; Q-73 to A-229; Q-73 to S-228; Q-73 to Y-227; Q-73 to C-226; Q-73 to S-225; Q-73 to N-224; Q-73 to N-223; Q-73 to P-222; Q-73 to L-221; Q-73 to T-220; Q-73 to E-219; Q-73 to P-218; Q-73 to M-217; Q-73 to N-216; Q-73 to Q-215; Q-73 to I-214; Q-73 to C-213; Q-73 to R-212; Q-73 to F-211; Q-73 to L-210; Q-73 to T-209; Q-73 to V-208; Q-73 to L-207; Q-73 to S-206; Q-73 to L-205; Q-73 to E-204; Q-73 to D-203; Q-73 to G-202; Q-73 to F-201; Q-73 to V-200; Q-73 to H-199; Q-73 to V-198; Q-73 to K-197; Q-73 to K-196; Q-73 to R-195; Q-73 to Q-194; Q-73 to I-193; Q-73 to L-192; Q-73 to H-191; Q-73 to G-190; Q-73 to Q-7389; Q-73 to A-188; Q-73 to Y-187; Q-73 to T-186; Q-73 to K-185; Q-73 to D-184; Q-73 to T-183; Q-73 to Y-182; Q-73 to L-181; Q-73 to V-180; Q-73 to Q-179; Q-73 to G-178; Q-73 to Y-177; Q-73 to I-176; Q-73 to F-175; Q-73 to F-174; Q-73 to Y-173; Q-73 to G-172; Q-73 to T-171; Q-73 to E-170; Q-73 to K-169; Q-73 to V-168; Q-73 to L-167; Q-73 to I-166; Q-73 to K-165; Q-73 to N-164; Q-73 to E-163; Q-73 to K-162; Q-73 to E-161; Q-73 to E-160; Q-73 to L-159; Q-73 to A-158; Q-73 to S-157; Q-73 to G-156; Q-73 to R-155; Q-73 to K-154; Q-73 to F-153; Q-73 to S-152; Q-73 to L-151; Q-73 to L-150; Q-73 to W-149; Q-73 to P-148; Q-73 to V-147; Q-73 to F-146; Q-73 to T-145; Q-73 to Y-144; Q-73 to S-143; Q-73 to G-142; Q-73 to T-141; Q-73 to E-140; Q-73 to E-139; Q-73 to P-138; Q-73 to G-137; Q-73 to Q-136; Q-73 to V-135; Q-73 to A-134; Q-73 to R-133; Q-73 to K-132; Q-73 to N-131; Q-73 to R-130; Q-73 to S-129; Q-73 to N-128; Q-73 to Q-127; Q-73 to S-126; Q-73 to S-125; Q-73 to N-124; Q-73 to G-123; Q-73 to E-122; Q-73 to G-121; Q-73 to P-120; Q-73 to A-119; Q-73 to P-118; Q-73 to P-117; Q-73 to E-116; Q-73 to F-115; Q-73 to I-114; Q-73 to K-113; Q-73 to L-112; Q-73 to G-111; Q-73 to A-110; Q-73 to T-109; Q-73 to V-108; Q-73 to A-107; Q-73 to P-106; Q-73 to A-105; Q-73 to E-104; Q-73 to E-103; Q-73 to L-102; Q-73 to G-101; Q-73 to A-100; Q-73 to K-99; Q-73 to P-98; Q-73 to A-97; Q-73 to G-96; Q-73 to A-95; Q-73 to G-94; Q-73 to A-93; Q-73 to P-92; Q-73 to L-91; Q-73 to K-90; Q-73 to E-89; Q-73 to A-88; Q-73 to H-87; Q-73 to H-86; Q-73 to G-85; Q-73 to Q-84; Q-73 to L-83; Q-73 to E-82; Q-73 to A-81; Q-73 to

R-80; Q-73 to L-79; and Q-73 to S-78 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0133] The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of the predicted extracellular domain of BLyS, which may be described generally as having residues n^4-m^4 of SEQ ID NO:3229 where n^4 and m^4 are integers as defined above.

[0134] In another embodiment, antibodies of the present invention bind polypeptides consisting of a portion of the extracellular domain of the BLyS amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518, where this portion excludes from 1 to about 260 amino acids from the amino terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or from 1 to about 187 amino acids from the carboxy terminus of the extracellular domain of the amino acid sequence encoded by cDNA clone contained in the deposit having ATCC Accession No. 203518, or any combination of the above amino terminal and carboxy terminal deletions, of the entire extracellular domain of the amino acid sequence encoded by the cDNA clone contained in the deposit having ATCC Accession No. 203518.

[0135] As mentioned above, even if deletion of one or more amino acids from the N-terminus of a polypeptide results in modification or loss of one or more functional activities (e.g., biological activity) of the polypeptide, other functional activities may still be retained. Thus, the ability of a shortened BLyS polypeptide to induce and/or bind to antibodies which recognize the full-length or mature forms or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the full-length or mature or extracellular domain of the polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted N-terminal amino acid residues may retain functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six

BLyS amino acid residues may often evoke an immune response.

[0136] Accordingly, the present invention further provides antibodies that bind polypeptides having one or more residues deleted from the amino terminus of the predicted full-length amino acid sequence of the BLyS polypeptide shown in SEQ ID NO:3229, up to the glycine residue at position number 261 of the sequence shown SEQ ID NO:3229 and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues n^5-266 of the sequence shown in SEQ ID NO:3229, where n^5 is an integer in the range of the amino acid position of amino acid residues 1 to 261 of the amino acid sequence in SEQ ID NO:3229.

[0137] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues of D-2 to L-266; D-3 to L-266; S-4 to L-266; T-5 to L-266; E-6 to L-266; R-7 to L-266; E-8 to L-266; Q-9 to L-266; S-10 to L-266; R-11 to L-266; L-12 to L-266; T-13 to L-266; S-14 to L-266; C-15 to L-266; L-16 to L-266; K-17 to L-266; K-18 to L-266; R-19 to L-266; E-20 to L-266; E-21 to L-266; M-22 to L-266; K-23 to L-266; L-24 to L-266; K-25 to L-266; E-26 to L-266; C-27 to L-266; V-28 to L-266; S-29 to L-266; I-30 to L-266; L-31 to L-266; P-32 to L-266; R-33 to L-266; K-34 to L-266; E-35 to L-266; S-36 to L-266; P-37 to L-266; S-38 to L-266; V-39 to L-266; R-40 to L-266; S-41 to L-266; S-42 to L-266; K-43 to L-266; D-44 to L-266; G-45 to L-266; K-46 to L-266; L-47 to L-266; L-48 to L-266; A-49 to L-266; A-50 to L-266; T-51 to L-266; L-52 to L-266; L-53 to L-266; L-54 to L-266; A-55 to L-266; L-56 to L-266; L-57 to L-266; S-58 to L-266; C-59 to L-266; C-60 to L-266; L-61 to L-266; T-62 to L-266; V-63 to L-266; V-64 to L-266; S-65 to L-266; F-66 to L-266; Y-67 to L-266; Q-68 to L-266; V-69 to L-266; A-70 to L-266; A-71 to L-266; L-72 to L-266; Q-73 to L-266; G-74 to L-266; D-75 to L-266; L-76 to L-266; A-77 to L-266; S-78 to L-266; L-79 to L-266; R-80 to L-266; A-81 to L-266; E-82 to L-266; L-83 to L-266; Q-84 to L-266; G-85 to L-266; H-86 to L-266; H-87 to L-266; A-88 to L-266; E-89 to L-266; K-90 to L-266; L-91 to L-266; P-92 to L-266; A-93 to L-266; G-94 to L-266; A-95 to L-266; G-96 to L-266; A-97 to L-266; P-98 to L-266; K-99 to L-266; A-100 to L-266; G-101 to L-266; L-102 to L-266; E-103 to L-266; E-104 to L-266; A-105 to L-266; P-106 to L-266; A-107 to L-266; V-108 to L-266; T-109 to L-266; A-110 to L-266; G-111 to L-266; L-112 to L-266; K-113 to

L-266; I-114 to L-266; F-115 to L-266; E-116 to L-266; P-117 to L-266; P-118 to L-266; A-119 to L-266; P-120 to L-266; G-121 to L-266; E-122 to L-266; G-123 to L-266; N-124 to L-266; S-125 to L-266; S-126 to L-266; Q-127 to L-266; N-128 to L-266; S-129 to L-266; R-130 to L-266; N-131 to L-266; K-132 to L-266; R-133 to L-266; A-134 to L-266; V-135 to L-266; Q-136 to L-266; G-137 to L-266; P-138 to L-266; E-139 to L-266; E-140 to L-266; T-141 to L-266; G-142 to L-266; S-143 to L-266; Y-144 to L-266; T-145 to L-266; F-146 to L-266; V-147 to L-266; P-148 to L-266; W-149 to L-266; L-150 to L-266; L-151 to L-266; S-152 to L-266; F-153 to L-266; K-154 to L-266; R-155 to L-266; G-156 to L-266; S-157 to L-266; A-158 to L-266; L-159 to L-266; E-160 to L-266; E-161 to L-266; K-162 to L-266; E-163 to L-266; N-164 to L-266; K-165 to L-266; I-166 to L-266; L-167 to L-266; V-168 to L-266; K-169 to L-266; E-170 to L-266; T-171 to L-266; G-172 to L-266; Y-173 to L-266; F-174 to L-266; F-175 to L-266; I-176 to L-266; Y-177 to L-266; G-178 to L-266; Q-179 to L-266; V-180 to L-266; L-181 to L-266; Y-182 to L-266; T-183 to L-266; D-184 to L-266; K-185 to L-266; T-186 to L-266; Y-187 to L-266; A-188 to L-266; M-189 to L-266; G-190 to L-266; H-191 to L-266; L-192 to L-266; I-193 to L-266; Q-194 to L-266; R-195 to L-266; K-196 to L-266; K-197 to L-266; V-198 to L-266; H-199 to L-266; V-200 to L-266; F-201 to L-266; G-202 to L-266; D-203 to L-266; E-204 to L-266; L-205 to L-266; S-206 to L-266; L-207 to L-266; V-208 to L-266; T-209 to L-266; L-210 to L-266; F-211 to L-266; R-212 to L-266; C-213 to L-266; I-214 to L-266; Q-215 to L-266; N-216 to L-266; M-217 to L-266; P-218 to L-266; E-219 to L-266; T-220 to L-266; L-221 to L-266; P-222 to L-266; N-223 to L-266; N-224 to L-266; S-225 to L-266; C-226 to L-266; Y-227 to L-266; S-228 to L-266; A-229 to L-266; G-230 to L-266; I-231 to L-266; A-232 to L-266; K-233 to L-266; L-234 to L-266; E-235 to L-266; E-236 to L-266; G-237 to L-266; D-238 to L-266; E-239 to L-266; L-240 to L-266; Q-241 to L-266; L-242 to L-266; A-243 to L-266; I-244 to L-266; P-245 to L-266; R-246 to L-266; E-247 to L-266; N-248 to L-266; A-249 to L-266; Q-250 to L-266; I-251 to L-266; S-252 to L-266; L-253 to L-266; D-254 to L-266; G-255 to L-266; D-256 to L-266; V-257 to L-266; T-258 to L-266; F-259 to L-266; F-260 to L-266; and G-261 to L-266 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0138] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more functional activities (e.g., biological activities) of the protein, other functional activities may still be retained. Thus, the ability of a shortened BLyS mutein to induce and/or bind to antibodies which recognize the complete or mature form or the extracellular domain of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature form or the extracellular domain of the polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a BLyS mutein with a large number of deleted C-terminal amino acid residues may retain some functional (e.g., immunogenic) activities. In fact, peptides composed of as few as six BLyS amino acid residues may often evoke an immune response.

[0139] Accordingly, the present invention further provides in another embodiment, antibodies that bind polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the BLyS shown in SEQ ID NO:3229, up to the glutamic acid residue at position number 6, and polynucleotides encoding such polypeptides. In particular, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 1-m^5 of SEQ ID NO:3229, where m^5 is an integer in the range of the amino acid position of amino acid residues 6 to 265 in the amino acid sequence of SEQ ID NO:3229.

[0140] More in particular, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues M-1 to L-265; M-1 to K-264; M-1 to L-263; M-1 to A-262; M-1 to G-261; M-1 to F-260; M-1 to F-259; M-1 to T-258; M-1 to V-257; M-1 to D-256; M-1 to G-255; M-1 to D-254; M-1 to L-253; M-1 to S-252; M-1 to I-251; M-1 to Q-250; M-1 to A-249; M-1 to N-248; M-1 to E-247; M-1 to R-246; M-1 to P-245; M-1 to I-244; M-1 to A-243; M-1 to L-242; M-1 to Q-241; M-1 to L-240; M-1 to E-239; M-1 to D-238; M-1 to G-237; M-1 to E-236; M-1 to E-235; M-1 to L-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to G-230; M-1 to A-229; M-1 to S-228; M-1 to Y-227; M-1 to C-226; M-1 to S-225; M-1 to N-224; M-1 to N-223; M-1 to P-222; M-1 to L-221; M-1 to T-220; M-1 to E-219; M-1 to P-218; M-1 to M-217; M-1 to N-216; M-1 to Q-215; M-1 to I-214; M-1 to

C-213; M-1 to R-212; M-1 to F-211; M-1 to L-210; M-1 to T-209; M-1 to V-208; M-1 to L-207; M-1 to S-206; M-1 to L-205; M-1 to E-204; M-1 to D-203; M-1 to G-202; M-1 to F-201; M-1 to V-200; M-1 to H-199; M-1 to V-198; M-1 to K-197; M-1 to K-196; M-1 to R-195; M-1 to Q-194; M-1 to I-193; M-1 to L-192; M-1 to H-191; M-1 to G-190; M-1 to M-189; M-1 to A-188; M-1 to Y-187; M-1 to T-186; M-1 to K-185; M-1 to D-184; M-1 to T-183; M-1 to Y-182; M-1 to L-181; M-1 to V-180; M-1 to Q-179; M-1 to G-178; M-1 to Y-177; M-1 to I-176; M-1 to F-175; M-1 to F-174; M-1 to Y-173; M-1 to G-172; M-1 to T-171; M-1 to E-170; M-1 to K-169; M-1 to V-168; M-1 to L-167; M-1 to I-166; M-1 to K-165; M-1 to N-164; M-1 to E-163; M-1 to K-162; M-1 to E-161; M-1 to E-160; M-1 to L-159; M-1 to A-158; M-1 to S-157; M-1 to G-156; M-1 to R-155; M-1 to K-154; M-1 to F-153; M-1 to S-152; M-1 to L-151; M-1 to L-150; M-1 to W-149; M-1 to P-148; M-1 to V-147; M-1 to F-146; M-1 to T-145; M-1 to Y-144; M-1 to S-143; M-1 to G-142; M-1 to T-141; M-1 to E-140; M-1 to E-139; M-1 to P-138; M-1 to G-137; M-1 to Q-136; M-1 to V-135; M-1 to A-134; M-1 to R-133; M-1 to K-132; M-1 to N-131; M-1 to R-130; M-1 to S-129; M-1 to N-128; M-1 to Q-127; M-1 to S-126; M-1 to S-125; M-1 to N-124; M-1 to G-123; M-1 to E-122; M-1 to G-121; M-1 to P-120; M-1 to A-119; M-1 to P-118; M-1 to P-117; M-1 to E-116; M-1 to F-115; M-1 to I-114; M-1 to K-113; M-1 to L-112; M-1 to G-111; M-1 to A-110; M-1 to T-109; M-1 to V-108; M-1 to A-107; M-1 to P-106; M-1 to A-105; M-1 to E-104; M-1 to E-103; M-1 to L-102; M-1 to G-101; M-1 to A-100; M-1 to K-99; M-1 to P-98; M-1 to A-97; M-1 to G-96; M-1 to A-95; M-1 to G-94; M-1 to A-93; M-1 to P-92; M-1 to L-91; M-1 to K-90; M-1 to E-89; M-1 to A-88; M-1 to H-87; M-1 to H-86; M-1 to G-85; M-1 to Q-84; M-1 to L-83; M-1 to E-82; M-1 to A-81; M-1 to R-80; M-1 to L-79; M-1 to S-78; M-1 to A-77; M-1 to L-76; M-1 to D-75; M-1 to G-74; M-1 to Q-73; M-1 to L-72; M-1 to A-71; M-1 to A-70; M-1 to V-69; M-1 to Q-68; M-1 to Y-67; M-1 to F-66; M-1 to S-65; M-1 to V-64; M-1 to V-63; M-1 to T-62; M-1 to L-61; M-1 to C-60; M-1 to C-59; M-1 to S-58; M-1 to L-57; M-1 to L-56; M-1 to A-55; M-1 to L-54; M-1 to L-53; M-1 to L-52; M-1 to T-51; M-1 to A-50; M-1 to A-49; M-1 to L-48; M-1 to L-47; M-1 to K-46; M-1 to G-45; M-1 to D-44; M-1 to K-43; M-1 to S-42; M-1 to S-41; M-1 to R-40; M-1 to V-39; M-1 to S-38; M-1 to P-37; M-1 to S-36; M-1 to E-35; M-1 to K-34; M-1 to R-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to S-29; M-1 to V-28; M-1 to C-27; M-1 to E-26; M-1 to K-25; M-1 to L-24; M-1 to K-23; M-1 to M-22; M-1 to E-21; M-1 to E-20; M-1 to R-19; M-1 to K-18; M-1 to K-17; M-1 to L-16; M-1 to C-15;

M-1 to S-14; M-1 to T-13; M-1 to L-12; M-1 to R-11; M-1 to S-10; M-1 to Q-9; M-1 to E-8; M-1 to R-7; and M-1 to E-6 of SEQ ID NO:3229. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0141] The invention also provides antibodies that bind polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini of a BLyS polypeptide, which may be described generally as having residues n^5-m^5 of SEQ ID NO:3229, where n^5 and m^5 are integers as defined above.

[0142] In additional embodiments, the present invention provides antibodies that bind polypeptides comprising the amino acid sequence of residues 134-m^6 of SEQ ID NO:3228, where m^6 is an integer from 140 to 285, corresponding to the position of the amino acid residue in SEQ ID NO:3228. For example, the invention provides antibodies that bind polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues A-134 to Leu-285; A-134 to L-284; A-134 to K-283; A-134 to L-282; A-134 to A-281; A-134 to G-280; A-134 to F-279; A-134 to F-278; A-134 to T-277; A-134 to V-276; A-134 to D-275; A-134 to G-274; A-134 to D-273; A-134 to L-272; A-134 to S-271; A-134 to I-270; A-134 to Q-269; A-134 to A-268; A-134 to N-267; A-134 to E-266; A-134 to R-265; A-134 to P-264; A-134 to I-263; A-134 to A-262; A-134 to L-261; A-134 to Q-260; A-134 to L-259; A-134 to E-258; A-134 to D-257; A-134 to G-256; A-134 to E-255; A-134 to E-254; A-134 to L-253; A-134 to K-252; A-134 to A-251; A-134 to I-250; A-134 to G-249; A-134 to A-248; A-134 to S-247; A-134 to Y-246; A-134 to C-245; A-134 to S-244; A-134 to N-243; A-134 to N-242; A-134 to P-241; A-134 to L-240; A-134 to T-239; A-134 to E-238; A-134 to P-237; A-134 to M-236; A-134 to N-235; A-134 to Q-234; A-134 to I-233; A-134 to C-232; A-134 to R-231; A-134 to F-230; A-134 to L-229; A-134 to T-228; A-134 to V-227; A-134 to L-226; A-134 to S-225; A-134 to L-224; A-134 to E-223; A-134 to D-222; A-134 to G-221; A-134 to F-220; A-134 to V-219; A-134 to H-218; A-134 to V-217; A-134 to K-216; A-134 to K-215; A-134 to R-214; A-134 to Q-213; A-134 to I-212; A-134 to L-211; A-134 to H-210; A-134 to G-209; A-134 to M-208; A-134 to A-207; A-134 to Y-206; A-134 to T-205; A-134 to K-204; A-134 to

D-203; A-134 to T-202; A-134 to Y-201; A-134 to L-200; A-134 to V-199; A-134 to Q-198; A-134 to G-197; A-134 to Y-196; A-134 to I-195; A-134 to F-194; A-134 to F-193; A-134 to Y-192; A-134 to G-191; A-134 to T-190; A-134 to E-189; A-134 to K-188; A-134 to V-187; A-134 to L-186; A-134 to I-185; A-134 to K-184; A-134 to N-183; A-134 to E-182; A-134 to K-181; A-134 to E-180; A-134 to E-179; A-134 to L-178; A-134 to A-177; A-134 to S-176; A-134 to G-175; A-134 to R-174; A-134 to K-173; A-134 to F-172; A-134 to S-171; A-134 to L-170; A-134 to L-169; A-134 to W-168; A-134 to P-167; A-134 to V-166; A-134 to F-165; A-134 to T-164; A-134 to Y-163; A-134 to S-162; A-134 to G-161; A-134 to K-160; A-134 to Q-159; A-134 to I-158; A-134 to T-157; A-134 to P-156; A-134 to T-155; A-134 to E-154; A-134 to S-153; A-134 to D-152; A-134 to A-151; A-134 to I-150; A-134 to L-149; A-134 to Q-148; A-134 to L-147; A-134 to C-146; A-134 to D-145; A-134 to Q-144; A-134 to T-143; A-134 to V-142; A-134 to T-141; and A-134 to E-140 of SEQ ID NO:3228. The present invention is also directed to antibodies that bind BLyS polypeptides comprising, or alternatively, consisting of, a contiguous sequence of amino acid residues at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of BLyS polypeptides described above.

[0143] In additional embodiments, antibodies of the present invention may bind polypeptide fragments comprising, or alternatively consisting of, an amino acid sequence selected from the group consisting of residues: M-1 to C-15; D-2 to L-16; D-3 to K-17; S-4 to K-18; T-5 to R-19; E-6 to E-20; R-7 to E-21; E-8 to M-22; Q-9 to K-23; S-10 to L-24; R-11 to K-25; L-12 to E-26; T-13 to C-27; S-14 to V-28; C-15 to S-29; L-16 to I-30; K-17 to L-31; K-18 to P-32; R-19 to R-33; E-20 to K-34; E-21 to E-35; M-22 to S-36; K-23 to P-37; L-24 to S-38; K-25 to V-39; E-26 to R-40; C-27 to S-41; V-28 to S-42; S-29 to K-43; I-30 to D-44; L-31 to G-45; P-32 to K-46; R-33 to L-47; K-34 to L-48; E-35 to A-49; S-36 to A-50; P-37 to T-51; S-38 to L-52; V-39 to L-53; R-40 to L-54; S-41 to A-55; S-42 to L-56; K-43 to L-57; D-44 to S-58; G-45 to C-59; K-46 to C-60; L-47 to L-61; L-48 to T-62; A-49 to V-63; A-50 to V-64; T-51 to S-65; L-52 to F-66; L-53 to Y-67; L-54 to Q-68; A-55 to V-69; L-56 to A-70; L-57 to A-71; S-58 to L-72; C-59 to Q-73; C-60 to G-74; L-61 to D-75; T-62 to L-76; V-63 to A-77; V-64 to S-78; S-65 to L-79; F-66 to R-80; Y-67 to A-81; Q-68 to E-82; V-69 to L-83; A-70 to Q-84; A-71 to G-85; L-72 to H-86; Q-73 to H-87; G-74 to A-88; D-75 to E-89; L-76 to K-90; A-77 to L-91; S-78 to P-92; L-79 to

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<210> 3022
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<400> 3022
Gln His Tyr Asp Ile Leu Thr Gly Tyr Ser Gln Glu Pro Phe Asp Ile
1 5 10 15

<210> 3023
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<400> 3023
Gly Glu Tyr Asp Ile Leu Thr Gly Tyr Pro Tyr Trp Tyr Phe Asp Leu
1 5 10 15

<210> 3024
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<400> 3024
Thr Tyr Tyr Asp Ile Leu Thr Gly Tyr Ser Gly Gly Gly Ala Phe Asp
1 5 10 15

Tyr

<210> 3025
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<212> PRT
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<400> 3025
Glu Ser Ser Ile Thr Val Asn Pro Pro Tyr Tyr Phe Tyr Gly Met Asp
1 5 10 15

Val

<210> 3026
<211> 14
<212> PRT
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<400> 3026
Pro Tyr Tyr Asp Ile Leu Thr Gly Tyr Phe Ala Phe Asp Ile
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<210> 3027
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<400> 3027
Glu Phe Asp Gln Leu Leu Ala Arg Gly His Gly Met Asp Val
1 5 10

<210> 3028
<211> 17
<212> PRT
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Ala Pro Leu Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile Gly Gly Asn Asp
1 5 10 15

Tyr

<210> 3029
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<212> PRT
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<400> 3029
Leu Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Arg Ser Asp Asp Tyr
1 5 10 15

<210> 3030
<211> 16
<212> PRT
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<400> 3030
Asp Ala Tyr Tyr Asp Ile Leu Thr Gly Trp Val Tyr Gly Met Asp Val
1 5 10 15

<210> 3031
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<212> PRT
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<400> 3031
Gly Arg His Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Glu Ala Phe
1 5 10 15

Asp Ile

<210> 3032
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<212> PRT
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<400> 3032
Ser Pro Gly Asp Asp Ile Leu Thr Gly Tyr Tyr Lys Tyr Tyr Phe Asp
1 5 10 15

Tyr

<210> 3033
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<212> PRT
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<400> 3033
Asp Arg Gly Pro Gly Leu Leu Ser Ser Phe Phe Glu Ser
1 5 10

<210> 3034
<211> 16
<212> PRT
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<400> 3034
Met Glu Tyr Asp Ile Leu Thr Ser Tyr Tyr Gly Gly Tyr Phe Asp Tyr
1 5 10 15

<210> 3035
<211> 19
<212> PRT
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<400> 3035
Gly Gly Leu Tyr Asp Ile Leu Thr Gly Arg Pro Ala Thr Asp Asp Ala
1 5 10 15

Phe Asp Ile

<210> 3036
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<400> 3036
Ser Pro Met Tyr Tyr Asp Arg Leu Thr Gly Phe Tyr Pro Ser Gly Tyr
1 5 10 15

Phe Asp Ser

<210> 3037
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<212> PRT
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<400> 3037
Gly Glu Gly Gly Tyr Asp Ile Leu Thr Gly Tyr Leu Arg Gly Tyr Gly
1 5 10 15

Met Asp Val

<210> 3038
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<212> PRT
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<400> 3038
Ser Gln Ser Asp Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 3039
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<212> PRT
<213> Homo sapiens

<400> 3039
Asp Arg Leu Glu Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr Tyr
1 5 10 15

Gly Met Asp Val
20

<210> 3040
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<212> PRT
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<400> 3040
Asp Lys Asp Tyr Asp Ile Leu Thr Gly Tyr Trp Arg Asp Glu Leu Leu
1 5 10 15

Asp Tyr

<210> 3041
<211> 16
<212> PRT
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<400> 3041
Glu Pro Tyr Asp Ile Leu Thr Gly Tyr Tyr Gly Ser Tyr Phe Asp Tyr
1 5 10 15

<210> 3042
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<212> PRT
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<400> 3042
Lys Asn Met Gly Ala Ser Ala Ala Ala Asp Phe
1 5 10

<210> 3043
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<400> 3043
Ala Arg Gly Ser Tyr Asp Ile Leu Thr Gly Tyr Tyr Arg Pro Gly Asp
1 5 10 15

Gly Tyr Phe Asp Tyr
20

<210> 3044
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<212> PRT
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Glu Ser Gly Ser His Tyr Asp Leu Leu Thr Gly Leu Leu Val Ala Ala
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Asn Gly Phe Asp Val
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<210> 3045
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Gly Glu Lys Ala Arg Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Ser Ala
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Trp Gly Gly Tyr Tyr Met Asp Val
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<212> PRT
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<400> 3046
Glu Lys Tyr Asp Ile Leu Thr Gly Tyr Tyr Asp Ala Phe Asp Ile
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<210> 3047
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<212> PRT
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<400> 3047
Asp Gln Val Asp Arg Leu Leu Met Gln Tyr Asn Tyr Tyr Met Asp Ala
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<210> 3048
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<212> PRT
<213> Homo sapiens

<400> 3048
Ala Gly Thr Ser Leu Met Asn Tyr Gly Thr Asp Val
1 5 10

<210> 3049
<211> 15
<212> PRT
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<400> 3049
Val Asn Tyr Asp Ile Leu Thr Gly Leu Gly Tyr Tyr Phe Asp Tyr
1 5 10 15

<210> 3050
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<212> PRT
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<400> 3050
Leu Pro Pro Tyr Asp Met Leu Thr Gly Tyr Tyr Val Gly Gly Gly Met
1 5 10 15

Asp Val

<210> 3051
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<212> PRT
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<400> 3051
Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Asp Ala Phe Asp Ile
1 5 10 15

<210> 3052
<211> 19
<212> PRT
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<400> 3052
Asp Lys Ser Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 3053
<211> 20
<212> PRT
<213> Homo sapiens

<400> 3053
Glu Arg Pro Gly Tyr Asp Ile Leu Thr Gly Tyr Pro Ser Ser Ile Tyr
1 5 10 15

Gly Met Asp Val

<210> 3054
<211> 13
<212> PRT
<213> Homo sapiens

<400> 3054
Asp Gln Phe Ser Val Gly Gly Arg His Ala Phe Asp Leu
1 5 10

<210> 3055
<211> 19
<212> PRT
<213> Homo sapiens

<400> 3055
Asp Val Thr Tyr His Asp Ile Leu Thr Gly Tyr Ala Gly His Glu Ala
1 5 10 15

Phe Asp Ile

<210> 3056
<211> 13
<212> PRT
<213> Homo sapiens

<400> 3056
Thr Tyr Tyr Asp Ile Leu Thr Gly Tyr Tyr Phe Asp Tyr
1 5 10

<210> 3057
<211> 18
<212> PRT
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<400> 3057
Gly Ser Gly Tyr Asp Val Leu Thr Gly Tyr Phe Thr Gly Ser Pro Leu
1 5 10 15

Asp Tyr

<210> 3058
<211> 16
<212> PRT
<213> Homo sapiens

<400> 3058
Ser Pro Tyr Asp Thr Leu Thr Gly Tyr Val Tyr Asn Gly Val Asp Val
1 5 10 15

<210> 3059
<211> 17
<212> PRT
<213> Homo sapiens

<400> 3059
Asp Gly Tyr Tyr Asp Ile Leu Thr Gly Tyr Ser Gly Tyr Tyr Met Asp
1 5 10 15

Val

<210> 3060
<211> 18
<212> PRT
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<400> 3060
Asp Arg Tyr Tyr Asp Ile Leu Thr Lys Gly Asp Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 3061
<211> 20
<212> PRT
<213> Homo sapiens

<400> 3061
Asp Arg Gly His Tyr Asp Ile Leu Thr Gly Tyr Tyr Ile Glu Pro Ser
1 5 10 15

Gly Phe Asp Tyr
20

<210> 3062
<211> 17
<212> PRT
<213> Homo sapiens

<400> 3062
Asp Pro Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Tyr Tyr Ala Met Asp
1 5 10 15

Val

<210> 3063

[0158]	Small	**[0172]** **[0173]** **[0174]** **[0175]** **[0176]**	Alanine Serine Threonine Methionine Glycine

[0177] In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLyS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 50 conservative amino acid substitutions, even more preferably, not more than 40 conservative amino acid substitutions, still more preferably, not more than 30 conservative amino acid substitutions, and still even more preferably, not more than 20 conservative amino acid substitutions. In one embodiment of the invention, antibodies of the present invention bind polypeptides comprising, or alternatively consisting of, the amino acid sequence of a BLyS polypeptide having an amino acid sequence which contains at least one conservative amino acid substitution, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 conservative amino acid substitutions.

[0178] For example, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of SEQ ID NO:3228 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with

A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S, T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A,

I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; V142 replaced with A, G, I, L, S, T, or M; T143 replaced with A, G, I, L, S, M, or V; Q144 replaced with N; D145 replaced with E; L147 replaced with A, G, I, S, T, M, or V; Q148 replaced with N; L149 replaced with A, G, I, S, T, M, or V; I150 replaced with A, G, L, S, T, M, or V; A151 replaced with G, I, L, S, T, M, or V; D152 replaced with E; S153 replaced with A, G, I, L, T, M, or V; E154 replaced with D; T155 replaced with A, G, I, L, S, M, or V; T157 replaced with A, G, I, L, S, M, or V; I158 replaced with A, G, L, S, T, M, or V; Q159 replaced with N; K160 replaced with H, or R; G161 replaced with A, I, L, S, T, M, or V; S162 replaced with A, G, I, L, T, M, or V; Y163 replaced with F, or W; T164 replaced with A, G, I, L, S, M, or V; F165 replaced with W, or Y; V166 replaced with A, G, I, L, S, T, or M; W168 replaced with F, or Y; L169 replaced with A, G, I, S, T, M, or V; L170 replaced with A, G, I, S, T, M, or V; S171 replaced with A, G, I, L, T, M, or V; F172 replaced with W, or Y; K173 replaced with H, or R; R174 replaced with H, or K; G175 replaced with A, I, L, S, T, M, or V; S176 replaced with A, G, I, L, T, M, or V; A177 replaced with G, I, L, S, T, M, or V; L178 replaced with A, G, I, S, T, M, or V; E179 replaced with D; E180 replaced with D; K181 replaced with H, or R; E182 replaced with D; N183 replaced with Q; K184 replaced with H, or R; I185 replaced with A, G, L, S, T, M, or V; L186 replaced with A, G, I, S, T, M, or V; V187 replaced with A, G, I, L, S, T, or M; K188 replaced with H, or R; E189 replaced with D; T190 replaced with A, G, I, L, S, M, or V; G191 replaced with A, I, L, S, T, M, or V; Y192 replaced with F, or W; F193 replaced with W, or Y; F194 replaced with W, or Y; I195 replaced with A, G, L, S, T, M, or V; Y196 replaced with F, or W; G197 replaced with A, I, L, S, T, M, or V; Q198 replaced with N; V199 replaced with A, G, I, L, S, T, or M; L200 replaced with A, G, I, S, T, M, or V; Y201 replaced with F, or W; T202 replaced with A, G, I, L, S, M, or V; D203 replaced with E; K204 replaced with H, or R; T205 replaced with A, G, I, L, S, M, or V; Y206 replaced with F, or W; A207 replaced with G, I, L, S, T, M, or V; M208 replaced with A, G, I, L, S, T, or V;

G209 replaced with A, I, L, S, T, M, or V; H210 replaced with K, or R; L211 replaced with A, G, I, S, T, M, or V; I212 replaced with A, G, L, S, T, M, or V; Q213 replaced with N; R214 replaced with H, or K; K215 replaced with H, or R; K216 replaced with H, or R; V217 replaced with A, G, I, L, S, T, or M; H218 replaced with K, or R; V219 replaced with A, G, I, L, S, T, or M; F220 replaced with W, or Y; G221 replaced with A, I, L, S, T, M, or V; D222 replaced with E; E223 replaced with D; L224 replaced with A, G, I, S, T, M, or V; S225 replaced with A, G, I, L, T, M, or V; L226 replaced with A, G, I, S, T, M, or V; V227 replaced with A, G, I, L, S, T, or M; T228 replaced with A, G, I, L, S, M, or V; L229 replaced with A, G, I, S, T, M, or V; F230 replaced with W, or Y; R231 replaced with H, or K; I233 replaced with A, G, L, S, T, M, or V; Q234 replaced with N; N235 replaced with Q; M236 replaced with A, G, I, L, S, T, or V; E238 replaced with D; T239 replaced with A, G, I, L, S, M, or V; L240 replaced with A, G, I, S, T, M, or V; N242 replaced with Q; N243 replaced with Q; S244 replaced with A, G, I, L, T, M, or V; Y246 replaced with F, or W; S247 replaced with A, G, I, L, T, M, or V; A248 replaced with G, I, L, S, T, M, or V; G249 replaced with A, I, L, S, T, M, or V; I250 replaced with A, G, L, S, T, M, or V; A251 replaced with G, I, L, S, T, M, or V; K252 replaced with H, or R; L253 replaced with A, G, I, S, T, M, or V; E254 replaced with D; E255 replaced with D; G256 replaced with A, I, L, S, T, M, or V; D257 replaced with E; E258 replaced with D; L259 replaced with A, G, I, S, T, M, or V; Q260 replaced with N; L261 replaced with A, G, I, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; I263 replaced with A, G, L, S, T, M, or V; R265 replaced with H, or K; E266 replaced with D; N267 replaced with Q; A268 replaced with G, I, L, S, T, M, or V; Q269 replaced with N; I270 replaced with A, G, L, S, T, M, or V; S271 replaced with A, G, I, L, T, M, or V; L272 replaced with A, G, I, S, T, M, or V; D273 replaced with E; G274 replaced with A, I, L, S, T, M, or V; D275 replaced with E; V276 replaced with A, G, I, L, S, T, or M; T277 replaced with A, G, I, L, S, M, or V; F278 replaced with W, or Y; F279 replaced with W, or Y; G280 replaced with A, I, L, S, T, M, or V; A281 replaced with G, I, L, S, T, M, or V; L282 replaced with A, G, I, S, T, M, or V; K283 replaced with H, or R; L284 replaced with A, G, I, S, T, M, or V; and/or L285 replaced with A, G, I, S, T, M, or V.

[0179] In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing

conservative substitution mutations of the polypeptide of SEQ ID NO:3229 including: M1 replaced with A, G, I, L, S, T, or V; D2 replaced with E; D3 replaced with E; S4 replaced with A, G, I, L, T, M, or V; T5 replaced with A, G, I, L, S, M, or V; E6 replaced with D; R7 replaced with H, or K; E8 replaced with D; Q9 replaced with N; S10 replaced with A, G, I, L, T, M, or V; R11 replaced with H, or K; L12 replaced with A, G, I, S, T, M, or V; T13 replaced with A, G, I, L, S, M, or V; S14 replaced with A, G, I, L, T, M, or V; L16 replaced with A, G, I, S, T, M, or V; K17 replaced with H, or R; K18 replaced with H, or R; R19 replaced with H, or K; E20 replaced with D; E21 replaced with D; M22 replaced with A, G, I, L, S, T, or V; K23 replaced with H, or R; L24 replaced with A, G, I, S, T, M, or V; K25 replaced with H, or R; E26 replaced with D; V28 replaced with A, G, I, L, S, T, or M; S29 replaced with A, G, I, L, T, M, or V; I30 replaced with A, G, L, S, T, M, or V; L31 replaced with A, G, I, S, T, M, or V; R33 replaced with H, or K; K34 replaced with H, or R; E35 replaced with D; S36 replaced with A, G, I, L, T, M, or V; S38 replaced with A, G, I, L, T, M, or V; V39 replaced with A, G, I, L, S, T, or M; R40 replaced with H, or K; S41 replaced with A, G, I, L, T, M, or V; S42 replaced with A, G, I, L, T, M, or V; K43 replaced with H, or R; D44 replaced with E; G45 replaced with A, I, L, S, T, M, or V; K46 replaced with H, or R; L47 replaced with A, G, I, S, T, M, or V; L48 replaced with A, G, I, S, T, M, or V; A49 replaced with G, I, L, S, T, M, or V; A50 replaced with G, I, L, S, T, M, or V; T51 replaced with A, G, I, L, S, M, or V; L52 replaced with A, G, I, S, T, M, or V; L53 replaced with A, G, I, S, T, M, or V; L54 replaced with A, G, I, S, T, M, or V; A55 replaced with G, I, L, S, T, M, or V; L56 replaced with A, G, I, S, T, M, or V; L57 replaced with A, G, I, S, T, M, or V; S58 replaced with A, G, I, L, T, M, or V; L61 replaced with A, G, I, S, T, M, or V; T62 replaced with A, G, I, L, S, M, or V; V63 replaced with A, G, I, L, S, T, or M; V64 replaced with A, G, I, L, S, T, or M; S65 replaced with A, G, I, L, T, M, or V; F66 replaced with W, or Y; Y67 replaced with F, or W; Q68 replaced with N; V69 replaced with A, G, I, L, S, T, or M; A70 replaced with G, I, L, S, T, M, or V; A71 replaced with G, I, L, S, T, M, or V; L72 replaced with A, G, I, S, T, M, or V; Q73 replaced with N; G74 replaced with A, I, L, S, T, M, or V; D75 replaced with E; L76 replaced with A, G, I, S, T, M, or V; A77 replaced with G, I, L, S, T, M, or V; S78 replaced with A, G, I, L, T, M, or V; L79 replaced with A, G, I, S, T, M, or V; R80 replaced with H, or K; A81 replaced with G, I, L, S, T, M, or V; E82 replaced with D; L83 replaced with A, G, I, S, T, M, or V; Q84 replaced with N; G85 replaced with A, I, L, S,

T, M, or V; H86 replaced with K, or R; H87 replaced with K, or R; A88 replaced with G, I, L, S, T, M, or V; E89 replaced with D; K90 replaced with H, or R; L91 replaced with A, G, I, S, T, M, or V; A93 replaced with G, I, L, S, T, M, or V; G94 replaced with A, I, L, S, T, M, or V; A95 replaced with G, I, L, S, T, M, or V; G96 replaced with A, I, L, S, T, M, or V; A97 replaced with G, I, L, S, T, M, or V; K99 replaced with H, or R; A100 replaced with G, I, L, S, T, M, or V; G101 replaced with A, I, L, S, T, M, or V; L102 replaced with A, G, I, S, T, M, or V; E103 replaced with D; E104 replaced with D; A105 replaced with G, I, L, S, T, M, or V; A107 replaced with G, I, L, S, T, M, or V; V108 replaced with A, G, I, L, S, T, or M; T109 replaced with A, G, I, L, S, M, or V; A110 replaced with G, I, L, S, T, M, or V; G111 replaced with A, I, L, S, T, M, or V; L112 replaced with A, G, I, S, T, M, or V; K113 replaced with H, or R; I114 replaced with A, G, L, S, T, M, or V; F115 replaced with W, or Y; E116 replaced with D; A119 replaced with G, I, L, S, T, M, or V; G121 replaced with A, I, L, S, T, M, or V; E122 replaced with D; G123 replaced with A, I, L, S, T, M, or V; N124 replaced with Q; S125 replaced with A, G, I, L, T, M, or V; S126 replaced with A, G, I, L, T, M, or V; Q127 replaced with N; N128 replaced with Q; S129 replaced with A, G, I, L, T, M, or V; R130 replaced with H, or K; N131 replaced with Q; K132 replaced with H, or R; R133 replaced with H, or K; A134 replaced with G, I, L, S, T, M, or V; V135 replaced with A, G, I, L, S, T, or M; Q136 replaced with N; G137 replaced with A, I, L, S, T, M, or V; E139 replaced with D; E140 replaced with D; T141 replaced with A, G, I, L, S, M, or V; G142 replaced with A, I, L, S, T, M, or V; S143 replaced with A, G, I, L, T, M, or V; Y144 replaced with F, or W; T145 replaced with A, G, I, L, S, M, or V; F146 replaced with W, or Y; V147 replaced with A, G, I, L, S, T, or M; W149 replaced with F, or Y; L150 replaced with A, G, I, S, T, M, or V; L151 replaced with A, G, I, S, T, M, or V; S152 replaced with A, G, I, L, T, M, or V; F153 replaced with W, or Y; K154 replaced with H, or R; R155 replaced with H, or K; G156 replaced with A, I, L, S, T, M, or V; S157 replaced with A, G, I, L, T, M, or V; A158 replaced with G, I, L, S, T, M, or V; L159 replaced with A, G, I, S, T, M, or V; E160 replaced with D; E161 replaced with D; K162 replaced with H, or R; E163 replaced with D; N164 replaced with Q; K165 replaced with H, or R; I166 replaced with A, G, L, S, T, M, or V; L167 replaced with A, G, I, S, T, M, or V; V168 replaced with A, G, I, L, S, T, or M; K169 replaced with H, or R; E170 replaced with D; T171 replaced with A, G, I, L, S, M, or V; G172 replaced with A, I, L, S, T, M, or V; Y173 replaced with F, or W; F174

replaced with W, or Y; F175 replaced with W, or Y; I176 replaced with A, G, L, S, T, M, or V; Y177 replaced with F, or W; G178 replaced with A, I, L, S, T, M, or V; Q179 replaced with N; V180 replaced with A, G, I, L, S, T, or M; L181 replaced with A, G, I, S, T, M, or V; Y182 replaced with F, or W; T183 replaced with A, G, I, L, S, M, or V; D184 replaced with E; K185 replaced with H, or R; T186 replaced with A, G, I, L, S, M, or V; Y187 replaced with F, or W; A188 replaced with G, I, L, S, T, M, or V; M189 replaced with A, G, I, L, S, T, or V; G190 replaced with A, I, L, S, T, M, or V; H191 replaced with K, or R; L192 replaced with A, G, I, S, T, M, or V; I193 replaced with A, G, L, S, T, M, or V; Q194 replaced with N; R195 replaced with H, or K; K196 replaced with H, or R; K197 replaced with H, or R; V198 replaced with A, G, I, L, S, T, or M; H199 replaced with K, or R; V200 replaced with A, G, I, L, S, T, or M; F201 replaced with W, or Y; G202 replaced with A, I, L, S, T, M, or V; D203 replaced with E; E204 replaced with D; L205 replaced with A, G, I, S, T, M, or V; S206 replaced with A, G, I, L, T, M, or V; L207 replaced with A, G, I, S, T, M, or V; V208 replaced with A, G, I, L, S, T, or M; T209 replaced with A, G, I, L, S, M, or V; L210 replaced with A, G, I, S, T, M, or V; F211 replaced with W, or Y; R212 replaced with H, or K; I214 replaced with A, G, L, S, T, M, or V; Q215 replaced with N; N216 replaced with Q; M217 replaced with A, G, I, L, S, T, or V; E219 replaced with D; T220 replaced with A, G, I, L, S, M, or V; L221 replaced with A, G, I, S, T, M, or V; N223 replaced with Q; N224 replaced with Q; S225 replaced with A, G, I, L, T, M, or V; Y227 replaced with F, or W; S228 replaced with A, G, I, L, T, M, or V; A229 replaced with G, I, L, S, T, M, or V; G230 replaced with A, I, L, S, T, M, or V; I231 replaced with A, G, L, S, T, M, or V; A232 replaced with G, I, L, S, T, M, or V; K233 replaced with H, or R; L234 replaced with A, G, I, S, T, M, or V; E235 replaced with D; E236 replaced with D; G237 replaced with A, I, L, S, T, M, or V; D238 replaced with E; E239 replaced with D; L240 replaced with A, G, I, S, T, M, or V; Q241 replaced with N; L242 replaced with A, G, I, S, T, M, or V; A243 replaced with G, I, L, S, T, M, or V; I244 replaced with A, G, L, S, T, M, or V; R246 replaced with H, or K; E247 replaced with D; N248 replaced with Q; A249 replaced with G, I, L, S, T, M, or V; Q250 replaced with N; I251 replaced with A, G, L, S, T, M, or V; S252 replaced with A, G, I, L, T, M, or V; L253 replaced with A, G, I, S, T, M, or V; D254 replaced with E; G255 replaced with A, I, L, S, T, M, or V; D256 replaced with E; V257 replaced with A, G, I, L, S, T, or M; T258 replaced with A, G, I, L, S, M, or V; F259 replaced with W, or Y; F260 replaced

with W, or Y; G261 replaced with A, I, L, S, T, M, or V; A262 replaced with G, I, L, S, T, M, or V; L263 replaced with A, G, I, S, T, M, or V; K264 replaced with H, or R; L265 replaced with A, G, I, S, T, M, or V; and/or L266 replaced with A, G, I, S, T, M, or V.

[0180] In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing conservative substitution mutations of the polypeptide of any one of SEQ ID NOS:3230-3237.

[0181] Amino acids in the BLyS polypeptides that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science 244*:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for functional activity, such ligand binding and the ability to stimulate lymphocyte (e.g., B cell) as, for example, proliferation, differentiation, and/or activation. Accordingly, antibodies of the present invention may bind amino acids in the BLyS polypeptides that are essential for function. In preferred embodiments, antibodies of the present invention bind amino acids in the BLyS polypeptides that are essential for function and inhibit BLyS polypeptide function. In other preferred embodiments, antibodies of the present invention bind amino acids in the BLyS polypeptides that are essential for function and enhance BLyS polypeptide function.

[0182] Of special interest are substitutions of charged amino acids with other charged or neutral amino acids which may produce proteins with highly desirable improved characteristics, such as less aggregation. Aggregation may not only reduce activity but also be problematic when preparing pharmaceutical formulations, because aggregates can be immunogenic (Pinckard *et al., Clin. Exp. Immunol. 2*:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland *et al., Crit. Rev. Therapeutic Drug Carrier Systems 10*:307-377 (1993).

[0183] In another embodiment, the invention provides for antibodies that bind polypeptides having amino acid sequences containing non-conservative substitutions of the amino acid sequence provided in SEQ ID NO:3228. For example, non-conservative substitutions of the BLyS protein sequence provided in SEQ ID NO:3228 include: M1 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D2 replaced with H, K, R, A, G, I, L,

S, T, M, V, N, Q, F, W, Y, P, or C; D3 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S4 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T5 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E6 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R7 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E8 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; Q9 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; S10 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R11 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L12 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T13 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S14 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C15 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L16 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K17 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K18 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; R19 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E20 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E21 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; M22 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K23 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L24 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K25 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E26 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; C27 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; V28 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S29 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; I30 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L31 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P32 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; R33 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K34 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; E35 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S36 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; P37 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or C; S38 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V39 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R40 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; S41 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S42 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; K43 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; D44 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; G45 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or

C; K46 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L47 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L48 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A49 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A50 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T51 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L52 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L53 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L54 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A55 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L56 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L57 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S58 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; C59 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; C60 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, or P; L61 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; T62 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V63 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; V64 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S65 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; F66 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Y67 replaced with D, E, H, K, R, N, Q, A, G, I, L, S, T, M, V, P, or C; Q68 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; V69 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A70 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A71 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L72 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q73 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G74 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; D75 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L76 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; A77 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; S78 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; L79 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; R80 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A81 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E82 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L83 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; Q84 replaced with D, E, H, K, R, A, G, I, L, S, T, M, V, F, W, Y, P, or C; G85 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; H86 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; H87 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; A88 replaced with D, E, H, K, R, N, Q, F, W, Y, P, or C; E89 replaced with H, K, R, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; K90 replaced with D, E, A, G, I, L, S, T, M, V, N, Q, F, W, Y, P, or C; L91 replaced with

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[0186] In another embodiment, site directed changes at the amino acid level of BLyS can be made by replacing a particular amino acid with a non-conservative substitution. Antibodies of the present invention may bind BLyS amino acid sequences containing non-conservative substitution mutations of the polypeptide of any one of SEQ

ID NOS:3230-3237.

[0187] In an additional embodiment, antibodies of the present invention bind BLyS polypeptides comprising, or alternatively consisting of, a BLyS amino acid sequence in which more than one amino acid (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30 and 50) is replaced with the substituted amino acids as described above (either conservative or nonconservative).

[0188] Replacement of amino acids can also change the selectivity of the binding of a ligand to cell surface receptors. For example, Ostade *et al., Nature 361*:266-268 (1993) describes certain mutations resulting in selective binding of TNF-alpha to only one of the two known types of TNF receptors. Since BLyS is a member of the TNF polypeptide family, mutations similar to those in TNF-alpha are likely to have similar effects in BLyS polypeptides.

[0189] Sites that are critical for ligand-receptor binding can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al., J. Mol. Biol. 224*:899-904 (1992) and de Vos *et al. Science 255*:306-312 (1992)).

[0190] Since BLyS is a member of the TNF-related protein family, mutations may be made in sequences encoding amino acids in the TNF conserved domain, e.g., in positions Gly-191 through Leu-284 of SEQ ID NO:3228 or in positions Gly-172 through Leu-265 of SEQ ID NO:3229, may modulate rather than completely eliminate functional activities (e.g., biological activities) of BLyS polypeptides or fragments or variants thereof. Accordingly, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain. In preferred embodiments, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain and act as antagonists of BLyS. In other preferred embodiments, antibodies of the present invention may bind BLyS polypeptides that have mutations in the TNF conserved domain and act as agonists of BLyS.

[0191] Recombinant DNA technology known to those skilled in the art (see, for instance, DNA shuffling *supra*) can be used to create novel mutant proteins or muteins including single or multiple amino acid substitutions, deletions, additions or fusion proteins. Such modified polypeptides can show, e.g., enhanced activity or increased stability. In addition, they may be purified in higher yields and show better solubility than

the corresponding natural polypeptide, at least under certain purification and storage conditions.

[0192] Thus, the invention also encompasses antibodies that bind BLyS derivatives and analogs that have one or more amino acid residues deleted, added, or substituted to generate BLyS polypeptides, e.g., that are better suited for expression, scale up, etc., in the host cells. For example, cysteine residues can be deleted or substituted with another amino acid residue in order to eliminate disulfide bridges; N-linked glycosylation sites can be altered or eliminated to achieve, for example, expression of a homogeneous product that is more easily recovered and purified from yeast hosts which are known to hyperglycosylate N-linked sites. To this end, a variety of amino acid substitutions at one or both of the first or third amino acid positions on any one or more of the glycosylation recognition sequences in the BLyS polypeptides of the invention, and/or an amino acid deletion at the second position of any one or more such recognition sequences will prevent glycosylation of the BLyS at the modified tripeptide sequence (see, e.g., Miyajimo et al., EMBO J 5(6):1193-1197). By way of non-limiting example, mutation of the serine at position 244 to alanine either singly or in combination with mutation of the asparagine at position 242 to glutamine abolishes glycosylation of the mature soluble form of BLyS (e.g., amino acids 134-285 of SEQ ID NO:3228) when expressed in the yeast *Pichea pastoris*. A mutant BLyS polypeptide in which only the asparagine at position 242 is mutated to glutamine, is still gycosylated when expressed in *Pichea pastoris*. In this mutant, the glycosylation event may be due to the activation or unmasking of an O-linked glyscosylation site at serine 244. Similar mutations affecting glycosylation could also be made in the BLyS polypeptide of SEQ ID NO:3229, i.e., aspargine-223 to glutamine and/or serine-224 to alanine of SEQ ID NO:3229. Additionally, one or more of the amino acid residues of the polypeptides of the invention (e.g., arginine and lysine residues) may be deleted or substituted with another residue to eliminate undesired processing by proteases such as, for example, furins or kexins. One possible result of such a mutation is that BLyS polypeptide of the invention is not cleaved and released from the cell surface. Accordingly, antibodies of the invention may bind BLyS derivatives and analogs that have one or more amino acid residues deleted, added, or substituted. In other embodiments, antibodies of the invention may bind BLyS derivatives, variants or analogs that are unable to be cleaved from the cell surface.

[0193] In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Lys-132 and/or Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, to prevent or diminish release of the soluble form of BLyS from cells expressing BLyS. In a more specific embodiment, antibodies of the invention bind BLyS polypeptides in which Lys-132 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to Ala-132. In another, nonexclusive specific embodiment, antibodies of the invention bind BLyS polypeptides in which Arg-133 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to Ala-133. These mutated proteins, and/or have uses such as, for example, in ex vivo therapy or gene therapy, to engineer cells expressing a BLyS polypeptide that is retained on the surface of the engineered cells.

[0194] In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-146 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-146 is replaced with a serine amino acid residue.

[0195] In another specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-232 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-232 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

[0196] In yet another specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-245 of the BLyS sequence shown in SEQ ID NO:3228 is mutated to another amino acid residue, or deleted altogether, for example, to aid preventing or diminishing oligomerization of the mutant BLyS polypeptide when expressed in an expression system. In a specific embodiment, antibodies of the invention bind BLyS polypeptides in which Cys-245 is replaced with a serine amino acid residue. Polypeptides encoding these polypeptides are also encompassed by the invention.

[0197] The polypeptides of the present invention are preferably provided in an

isolated form, and preferably are substantially purified. A recombinantly produced version of the BLyS polypeptides can be substantially purified by the one-step method described in Smith and Johnson, *Gene 67*:31-40 (1988).

[0198] The antibodies of the present invention bind BLyS polypeptides including the complete polypeptide encoded by the deposited cDNA (ATCC Deposit No. 97768) including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA, the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3228, the mature soluble polypeptide of SEQ ID NO:3228, e.g., amino acids 134-285 of SEQ ID NO:3228, the extracellular domain of SEQ ID NO:3228, amino acid residues 73-285 of SEQ ID NO:3228 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0199] The antibodies of the present invention bind BLyS polypeptides including the complete polypeptide encoded by the deposited cDNA including the intracellular, transmembrane and extracellular domains of the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 203518), the mature soluble polypeptide encoded by the deposited cDNA, the extracellular domain minus the intracellular and transmembrane domains of the protein, the complete polypeptide of SEQ ID NO:3229, the mature soluble of SEQ ID NO:3229, e.g., amino acid residues 134-266 of SEQ ID NO:3229, the extracellular domain of SEQ ID NO:3229, e.g., amino acid residues 73-266 of SEQ ID NO:3229 minus the intracellular and transmembrane domains, as well as polypeptides which have at least 80%, 85%, 90% similarity, more preferably at least 95% similarity, and still more preferably at least 96%, 97%, 98% or 99% similarity to those described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0200] Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 97768) or to the polypeptide of SEQ

ID NO:3228, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids.

[0201] Further antibodies of the present invention bind polypeptides including polypeptides at least 80%, or at least 85% identical, more preferably at least 90% or 95% identical, still more preferably at least 96%, 97%, 98% or 99% identical to the polypeptide encoded by the deposited cDNA (ATCC Deposit No. 203518) or to the polypeptide of SEQ ID NO:3229, and also include antibodies that bind portions of such polypeptides with at least 30 amino acids and more preferably at least 50 amino acids. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0202] By "% similarity" for two polypeptides is intended a similarity score produced by comparing the amino acid sequences of the two polypeptides using the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711) and the default settings for determining similarity. Bestfit uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics 2:482-489, 1981) to find the best segment of similarity between two sequences.

[0203] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a reference amino acid sequence of a BLyS polypeptide is intended that the amino acid sequence of the polypeptide is identical to the reference sequence except that the polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the reference amino acid of the BLyS polypeptide. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a reference amino acid sequence, up to 5% of the amino acid residues in the reference sequence may be deleted or substituted with another amino acid, or a number of amino acids up to 5% of the total amino acid residues in the reference sequence may be inserted into the reference sequence. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0204] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of SEQ ID NO:3228, the amino acid sequence encoded by the deposited cDNA

clone HNEDU15 (ATCC Accession No. 97768), or fragments thereof, or, for instance, to the amino acid sequence of SEQ ID NO:3229, the amino acid sequence encoded by the deposited cDNA clone HDPMC52 (ATCC Accession No. 203518), or fragments thereof, can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

[0205] In a specific embodiment, the identity between a reference (query) sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, is determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter. According to this embodiment, if the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction is made to the results to take into consideration the fact that the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. A determination of whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is

what is used for the purposes of this embodiment. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence. For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are made for the purposes of this embodiment.

[0206] Antibodies that Immunospecifically bind BLyS Polypeptides

[0207] The present invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that immunospecifically bind to BLyS polypeptides, which antibodies comprise, or alternatively consist of, all or a portion of a heavy and/or light chain variable domain of the scFvs referred to in Table 1.

[0208] The present invention also encompasses methods and compositions for detecting, diagnosing and/or prognosing diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising using antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can

be detected, diagnosed or prognosed with the antibodies of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0209] The present invention further encompasses methods and compositions for preventing, treating or ameliorating diseases or disorders associated with aberrant BLyS or BLyS receptor expression or inappropriate BLyS or BLyS receptor function in an animal, preferably a mammal, and most preferably a human, comprising administering to said animal an effective amount of one or more antibodies (including molecules which comprise, or alternatively consist of, antibody fragments or variants thereof) that immunospecifically bind to BLyS. Diseases and disorders which can be prevented, treated or inhibited by administering an effective amount of one or more antibodies or molecules of the invention include, but are not limited to, immune disorders (*e.g.*, lupus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis, Hashimoto's disease, and immunodeficiency syndrome), inflammatory disorders (*e.g.*, asthma, allergic disorders, and rheumatoid arthritis), infectious diseases (*e.g.*, AIDS), and proliferative disorders (*e.g.*, leukemia, carcinoma, and lymphoma).

[0210] Anti-BLyS Antibodies

[0211] The antibodies of the present invention were discovered, in part, using phage display technology. Single chain antibody molecules ("scFvs") displayed on the surface of phage particles were screened to identify those scFvs that immunospecifically bind to BLyS, including the membrane-bound form and soluble form of BLyS. The present invention encompasses the scFvs and portions thereof that were identified to immunospecifically bind to BLyS, including scFvs that immunospecifically bind to the soluble form of BLyS, scFvs that immunospecifically bind to the membrane-bound form of BLyS, and scFvs that immunospecifically bind to both the soluble form and membrane-bound form of BLyS. In particular, the present invention encompasses scFvs comprising, or alternatively consisting of, the amino acid sequence of SEQ ID NOS: 1 - 2128, as referred to in Table 1. Preferably, the scFvs of the present invention comprise, or alternatively consist of, the amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 834 -

872, 1563 - 1595, or 1881 - 1908. The scFvs include scFvs that bind to soluble BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1563 - 1880), scFvs that bind to the membrane-bound form of BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1881 - 2128), and scFvs that bind to both the soluble form and the membrane-bound form of BLyS (e.g., scFvs comprising, or alternatively consisting of, an amino acid sequence of SEQ ID NOS: 1 - 1562). Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0212] In one embodiment of the present invention, scFvs that immunospecifically bind to BLyS comprise a polypeptide having the amino acid sequence of any one of the VH domains referred to in Table 1 and/or any one of the VL domains referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1 and/or any one, two, three, or more of the VL CDRs referred to in Table 1. In preferred embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention comprise the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, antibody fragments or variants of the scFvs referred to in Table 1 that immunospecifically bind to BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0213] (Table 1 can be found at the end of the specification just prior to the claims.)

[0214] In another embodiment of the present invention, an scFv that immunospecifically binds to a soluble form of BLyS, comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 – 1880 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1570 - 1595. In an even more preferred embodiment, an scFv that immunospecifically binds to a soluble form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1563 - 1569.

[0215] In another embodiment of the present invention, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 2128 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1886 - 1908. In an even more preferred embodiment, an scFv that immunospecifically binds to a membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1881 - 1885.

[0216] In another embodiment of the present invention, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:1 - 1562 as referred to in Table 1. In a preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, the amino acid sequence of SEQ ID NOS:834 - 872. In another preferred embodiment, an scFv that immunospecifically binds to both the soluble form and membrane-bound form of BLyS comprises, or alternatively consists of, any one of the amino acids sequences of SEQ ID NOS:1 – 46 or 321 - 329. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to the soluble form of BLyS and/or the membrane-bound form of BLyS are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0217] In another embodiment of the present invention, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1563 –

1880 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in contained SEQ ID NOS:1563 - 1880, as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the of the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS:1563 - 1880 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1563 - 1880 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS, preferably the soluble form of BLyS, are also encompassed by the invention, as are nucleic acid molecules encoding these scFvs, molecules, fragments and/or variants.

[0218] In another embodiment of the present invention, scFvs that

immunospecifically bind to the membrane-bound form of BLyS comprise a polypeptide having the amino acid sequence of any one of the VH domains contained in SEQ ID NOS:1881 - 2128 as disclosed in Table 1 and/or any one of the VL domains contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the soluble form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In another embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one, two, three, or more of the VL CDRs contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from different scFvs referred to in Table 1. In a preferred embodiment, scFvs that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of any one of the VH CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1 and/or any one of the VL CDR3s contained in SEQ ID NOS: 1881 - 2128 as disclosed in Table 1. In preferred embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH domain and VL domain from the same scFv referred to in Table 1. In alternative embodiments, scFvs of the present invention that immunospecifically bind to the membrane-bound form of BLyS, comprise a polypeptide having the amino acid sequence of a VH CDR and VL CDR from different scFvs referred to in Table 1. Molecules comprising, or alternatively consisting of, fragments or variants of these scFvs, that immunospecifically bind to BLyS, preferably the membrane-bound form of BLyS, are

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<211> 10
<212> PRT
<213> Homo sapiens

<400> 3201
Asp Glu Tyr Ser Ser Leu Tyr Met Asp Val
1 5 10

<210> 3202
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3202
Ser Asn Trp Gly Gly Asp Ala Phe Asp Ile
1 5 10

<210> 3203
<211> 17
<212> PRT
<213> Homo sapiens

<400> 3203
Glu Ser Ser Gly Thr Leu Gly Glu Phe Ser Leu Glu Leu Pro Phe Asp
1 5 10 15

Tyr

<210> 3204
<211> 14
<212> PRT
<213> Homo sapiens

<400> 3204
Thr Ser Glu Arg Gly Thr Tyr Arg Gln Trp Asp Phe Asp Asn
1 5 10

<210> 3205
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3205
His Asp Val Tyr Gly Asp Leu Phe Asp Ser

1 5 10

<210> 3206
<211> 12
<212> PRT
<213> Homo sapiens

<400> 3206
Leu Gly Val Ala Arg Gly Arg Glu Ala Phe Asp Leu
1 5 10

<210> 3207
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3207
Asp Gln Gly Ile Glu Thr Ala Asn Asp Tyr
1 5 10

<210> 3208
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3208
Ser Val Ala Gly Arg Gly Asn Phe Asp Tyr
1 5 10

<210> 3209
<211> 13
<212> PRT
<213> Homo sapiens

<400> 3209
Arg Gly Gly Thr Ser Glu Asn Tyr Ser Gly Met Asp Val
1 5 10

<210> 3210
<211> 6
<212> PRT
<213> Homo sapiens

<400> 3210
Gly Gly Trp Leu Asp Asp
1 5

<210> 3211
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3211

His Asp Val Tyr Gly Asp Leu Phe Asp Tyr
1 5 10

<210> 3212
<211> 16
<212> PRT
<213> Homo sapiens

<400> 3212
Glu Thr Phe Ser His Cys Ser Gly Gly Ser Cys Tyr Pro Phe Asp Tyr
1 5 10 15

<210> 3213
<211> 9
<212> PRT
<213> Homo sapiens

<400> 3213
Val Asp Ser Ser Gly Tyr Ala Tyr Tyr
1 5

<210> 3214
<211> 8
<212> PRT
<213> Homo sapiens

<400> 3214
Ser Ser Arg Asn Gly Gly Asp Tyr
1 5

<210> 3215
<211> 14
<212> PRT
<213> Homo sapiens

<400> 3215
Arg Thr Pro Asp His Asn Gly Asp Ser Gly Pro Pro Asp Tyr
1 5 10

<210> 3216
<211> 6
<212> PRT
<213> Homo sapiens

<400> 3216
Val His Ser Ser Gly Ser
1 5

<210> 3217
<211> 12
<212> PRT
<213> Homo sapiens

<400> 3217
Gly Lys Arg Tyr Ser Tyr Gly Trp Tyr Phe Asp Val
1 5 10

<210> 3218
<211> 14
<212> PRT
<213> Homo sapiens

<400> 3218
Leu Arg Pro Asp Ala Asp Tyr Gly Asp Tyr Gly Phe Asp Tyr
1 5 10

<210> 3219
<211> 21
<212> PRT
<213> Homo sapiens

<400> 3219
Leu Pro Pro Asp Leu Arg Tyr Cys Asp Gly Gly Met Cys Ser Gly Phe
1 5 10 15

Asp Trp Leu Gly Pro
20

<210> 3220
<211> 11
<212> PRT
<213> Homo sapiens

<400> 3220
Asp Gly Thr Lys Tyr Asp Trp Gly Phe Asp Tyr
1 5 10

<210> 3221
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3221
Leu His Cys Ser Gly Gly Ser Cys Gly Phe
1 5 10

<210> 3222
<211> 18
<212> PRT
<213> Homo sapiens

<400> 3222
Gly Pro Ile Tyr Tyr Phe Asp Gly Ser Ala Tyr Glu Gly Tyr Tyr Phe
1 5 10 15

Asp Tyr

<210> 3223
<211> 8
<212> PRT
<213> Homo sapiens

<400> 3223
Met Asn Ala Asp Ala Phe Glu Ile
1 5

<210> 3224
<211> 10
<212> PRT
<213> Homo sapiens

<400> 3224
Phe Gly Ala Gly Arg Leu Tyr Asp Asp Tyr
1 5 10

<210> 3225
<211> 15
<212> PRT
<213> Homo sapiens

<400> 3225
Ala Gly Gly Asn Pro Arg Ser Gly Ser Leu Val Tyr Phe Asp Tyr
1 5 10 15

<210> 3226
<211> 19
<212> PRT
<213> Homo sapiens

<400> 3226
Gly Gly Arg Tyr Gly Tyr Tyr Tyr Asp Gly Thr Gly Tyr Val Asp Ala
1 5 10 15

Phe Asp Ile

<210> 3227
<211> 19
<212> PRT
<213> Homo sapiens

<400> 3227
Asp Tyr Tyr Asp Gly Ser Ser Tyr Ser Ser Gly Asp Tyr Tyr Tyr Tyr
1 5 10 15

Met Asp Val

<210> 3228
<211> 285
<212> PRT
<213> Homo sapiens

<400> 3228

Met Asp Asp Ser Thr Glu Arg Glu Gln Ser Arg Leu Thr Ser Cys Leu
1 5 10 15

Lys Lys Arg Glu Glu Met Lys Leu Lys Glu Cys Val Ser Ile Leu Pro
20 25 30

Arg Lys Glu Ser Pro Ser Val Arg Ser Ser Lys Asp Gly Lys Leu Leu
35 40 45

Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Cys Cys Leu Thr Val Val
50 55 60

Ser Phe Tyr Gln Val Ala Ala Leu Gln Gly Asp Leu Ala Ser Leu Arg
65 70 75 80

Ala Glu Leu Gln Gly His His Ala Glu Lys Leu Pro Ala Gly Ala Gly
85 90 95

Ala Pro Lys Ala Gly Leu Glu Glu Ala Pro Ala Val Thr Ala Gly Leu
100 105 110

Lys Ile Phe Glu Pro Pro Ala Pro Gly Glu Gly Asn Ser Ser Gln Asn
115 120 125

Ser Arg Asn Lys Arg Ala Val Gln Gly Pro Glu Glu Thr Val Thr Gln
130 135 140

Asp Cys Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys
145 150 155 160

Gly Ser Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser
165 170 175

Ala Leu Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr
180 185 190

Phe Phe Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met
195 200 205

Gly His Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu
210 215 220

Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu
225 230 235 240

Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly
245 250 255

Asp Glu Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu

260 265 270

Asp Gly Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu
275 280 285

<210> 3229
<211> 266
<212> PRT
<213> Human sapiens

<400> 3229

Met Asp Asp Ser Thr Glu Arg Glu Gln Ser Arg Leu Thr Ser Cys Leu
1 5 10 15

Lys Lys Arg Glu Glu Met Lys Leu Lys Glu Cys Val Ser Ile Leu Pro
20 25 30

Arg Lys Glu Ser Pro Ser Val Arg Ser Ser Lys Asp Gly Lys Leu Leu
35 40 45

Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Cys Cys Leu Thr Val Val
50 55 60

Ser Phe Tyr Gln Val Ala Ala Leu Gln Gly Asp Leu Ala Ser Leu Arg
65 70 75 80

Ala Glu Leu Gln Gly His His Ala Glu Lys Leu Pro Ala Gly Ala Gly
85 90 95

Ala Pro Lys Ala Gly Leu Glu Glu Ala Pro Ala Val Thr Ala Gly Leu
100 105 110

Lys Ile Phe Glu Pro Pro Ala Pro Gly Glu Gly Asn Ser Ser Gln Asn
115 120 125

Ser Arg Asn Lys Arg Ala Val Gln Gly Pro Glu Glu Thr Gly Ser Tyr
130 135 140

Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser Ala Leu Glu
145 150 155 160

Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr Phe Phe Ile
165 170 175

Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met Gly His Leu
180 185 190

Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu Ser Leu Val
195 200 205

Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu Pro Asn Asn
210 215 220

Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp Glu Leu
225 230 235 240

Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu Asp Gly Asp
245 250 255

Val Thr Phe Phe Gly Ala Leu Lys Leu Leu
260 265

<210> 3230
<211> 309
<212> PRT
<213> Mus musculus

<400> 3230

Met Asp Glu Ser Ala Lys Thr Leu Pro Pro Pro Cys Leu Cys Phe Cys
1 5 10 15

Ser Glu Lys Gly Glu Asp Met Lys Val Gly Tyr Asp Pro Ile Thr Pro
20 25 30

Gln Lys Glu Glu Gly Ala Trp Phe Gly Ile Cys Arg Asp Gly Arg Leu
35 40 45

Leu Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Ser Ser Phe Thr Ala
50 55 60

Met Ser Leu Tyr Gln Leu Ala Ala Leu Gln Ala Asp Leu Met Asn Leu
65 70 75 80

Arg Met Glu Leu Gln Ser Tyr Arg Gly Ser Ala Thr Pro Ala Ala Ala
85 90 95

Gly Ala Pro Glu Leu Thr Ala Gly Val Lys Leu Leu Thr Pro Ala Ala
100 105 110

Pro Arg Pro His Asn Ser Ser Arg Gly His Arg Asn Arg Arg Ala Phe
115 120 125

Gln Gly Pro Glu Glu Thr Glu Gln Asp Val Asp Leu Ser Ala Pro Pro
130 135 140

Ala Pro Cys Leu Pro Gly Cys Arg His Ser Gln His Asp Asp Asn Gly
145 150 155 160

Met Asn Leu Arg Asn Ile Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp
165 170 175

Ser Asp Thr Pro Thr Ile Arg Lys Gly Thr Tyr Thr Phe Val Pro Trp
180 185 190

Leu Leu Ser Phe Lys Arg Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys
195 200 205

Ile Val Val Arg Gln Thr Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu
210 215 220

Tyr Thr Asp Pro Ile Phe Ala Met Gly His Val Ile Gln Arg Lys Lys
225 230 235 240

Val His Val Phe Gly Asp Glu Leu Ser Leu Val Thr Leu Phe Arg Cys
245 250 255

Ile Gln Asn Met Pro Lys Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala
260 265 270

Gly Ile Ala Arg Leu Glu Glu Gly Asp Glu Ile Gln Leu Ala Ile Pro
275 280 285

Arg Glu Asn Ala Gln Ile Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly
290 295 300

Ala Leu Lys Leu Leu
305

<210> 3231
<211> 290
<212> PRT
<213> Mus musculus

<400> 3231

Met Asp Glu Ser Ala Lys Thr Leu Pro Pro Pro Cys Leu Cys Phe Cys
1 5 10 15

Ser Glu Lys Gly Glu Asp Met Lys Val Gly Tyr Asp Pro Ile Thr Pro
20 25 30

Gln Lys Glu Glu Gly Ala Trp Phe Gly Ile Cys Arg Asp Gly Arg Leu
35 40 45

Leu Ala Ala Thr Leu Leu Leu Ala Leu Leu Ser Ser Ser Phe Thr Ala
50 55 60

Met Ser Leu Tyr Gln Leu Ala Ala Leu Gln Ala Asp Leu Met Asn Leu
65 70 75 80

Arg Met Glu Leu Gln Ser Tyr Arg Gly Ser Ala Thr Pro Ala Ala Ala
85 90 95

Gly Ala Pro Glu Leu Thr Ala Gly Val Lys Leu Leu Thr Pro Ala Ala
100 105 110

Pro Arg Pro His Asn Ser Ser Arg Gly His Arg Asn Arg Arg Ala Phe
115 120 125

Gln Gly Pro Glu Glu Thr Glu Gln Asp Val Asp Leu Ser Ala Pro Pro
130 135 140

Ala Pro Cys Leu Pro Gly Cys Arg His Ser Gln His Asp Asp Asn Gly
145 150 155 160

Met Asn Leu Arg Asn Arg Thr Tyr Thr Phe Val Pro Trp Leu Leu Ser
165 170 175

Phe Lys Arg Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys Ile Val Val
180 185 190

Arg Gln Thr Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu Tyr Thr Asp
195 200 205

Pro Ile Phe Ala Met Gly His Val Ile Gln Arg Lys Lys Val His Val

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    210                 215                 220

Phe Gly Asp Glu Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn
225                 230                 235                 240

Met Pro Lys Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala
                245                 250                 255

Arg Leu Glu Glu Gly Asp Glu Ile Gln Leu Ala Ile Pro Arg Glu Asn
            260                 265                 270

Ala Gln Ile Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly Ala Leu Lys
        275                 280                 285

Leu Leu
    290
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<210> 3232
<211> 239
<212> PRT
<213> Rattus rattus

<400> 3232

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Ala Val Gln Ala Asp Leu Met Ser Leu Arg Met Glu Leu Gln Ser Tyr
1               5                   10                  15

Arg Ser Ser Ala Thr Pro Ala Ala Pro Gly Ala Pro Gly Leu Ser Ala
            20                  25                  30

Gly Val Lys Leu Pro Thr Pro Ala Ala Pro Gly Pro His Asn Ser Ser
        35                  40                  45

Arg Gly Gln Arg Asn Arg Arg Ala Phe Gln Gly Pro Glu Glu Thr Glu
    50                  55                  60

Gln Asp Val Asp Leu Ser Ala Thr Pro Ala Pro Ser Leu Pro Gly Asn
65                  70                  75                  80

Cys His Ala Ser His His Asp Glu Asn Gly Leu Asn Leu Arg Thr Ile
                85                  90                  95

Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp Ser Asn Thr Pro Thr Ile
            100                 105                 110

Arg Lys Gly Thr Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg
        115                 120                 125

Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys Ile Val Val Arg Gln Thr
    130                 135                 140

Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu Tyr Thr Asp Pro Ile Phe
145                 150                 155                 160

Ala Met Gly His Val Ile Gln Arg Lys Lys Ile His Val Phe Gly Asp
                165                 170                 175

Glu Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Lys
            180                 185                 190
```

Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu
195 200 205

Glu Gly Asp Glu Ile Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile
210 215 220

Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly Ala Leu Lys Leu Leu
225 230 235

<210> 3233
<211> 220
<212> PRT
<213> Rattus rattus

<400> 3233

Ala Val Gln Ala Asp Leu Met Ser Leu Arg Met Glu Leu Gln Ser Tyr
1 5 10 15

Arg Ser Ser Ala Thr Pro Ala Ala Pro Gly Ala Pro Gly Leu Ser Ala
20 25 30

Gly Val Lys Leu Pro Thr Pro Ala Ala Pro Gly Pro His Asn Ser Ser
35 40 45

Arg Gly Gln Arg Asn Arg Arg Ala Phe Gln Gly Pro Glu Glu Thr Glu
50 55 60

Gln Asp Val Asp Leu Ser Ala Thr Pro Val Pro Ser Leu Pro Gly Asn
65 70 75 80

Cys His Ala Ser His His Asp Glu Asn Gly Leu Asn Leu Arg Thr Arg
85 90 95

Thr Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Asn Ala
100 105 110

Leu Glu Glu Lys Glu Asn Lys Ile Val Val Arg Gln Thr Gly Tyr Phe
115 120 125

Phe Ile Tyr Ser Gln Val Leu Tyr Thr Asp Pro Ile Phe Ala Met Gly
130 135 140

His Val Ile Gln Arg Lys Lys Ile His Val Phe Gly Asp Glu Leu Ser
145 150 155 160

Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Lys Thr Leu Pro
165 170 175

Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp
180 185 190

Glu Ile Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Arg Asn
195 200 205

Gly Asp Asp Thr Phe Phe Gly Ala Leu Lys Leu Leu
210 215 220

<210> 3234
<211> 207
<212> PRT
<213> Rattus rattus

<400> 3234

Ala Val Gln Ala Asp Leu Met Ser Leu Arg Met Glu Leu Gln Ser Tyr
1 5 10 15

Arg Ser Ser Ala Thr Pro Ala Ala Pro Gly Ala Pro Gly Leu Ser Ala
20 25 30

Gly Val Lys Leu Pro Thr Pro Ala Ala Pro Gly Pro His Asn Ser Ser
35 40 45

Arg Gly Gln Arg Asn Arg Arg Ala Phe Gln Gly Pro Glu Glu Thr Val
50 55 60

Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp Ser Asn Thr Pro Thr Ile
65 70 75 80

Arg Lys Gly Thr Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg
85 90 95

Gly Asn Ala Leu Glu Glu Lys Glu Asn Lys Ile Val Val Arg Gln Thr
100 105 110

Gly Tyr Phe Phe Ile Tyr Ser Gln Val Leu Tyr Thr Asp Pro Ile Phe
115 120 125

Ala Met Gly His Val Ile Gln Arg Lys Lys Ile His Val Phe Gly Asp
130 135 140

Glu Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Lys
145 150 155 160

Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu
165 170 175

Glu Gly Asp Glu Val Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile
180 185 190

Ser Arg Asn Gly Asp Asp Thr Phe Phe Gly Ala Leu Lys Leu Leu
195 200 205

<210> 3235
<211> 188
<212> PRT
<213> Rattus rattus

<400> 3235

Ala Val Gln Ala Asp Leu Met Ser Leu Arg Met Glu Leu Gln Ser Tyr
1 5 10 15

Arg Ser Ser Ala Thr Pro Ala Ala Pro Gly Ala Pro Gly Leu Ser Ala
20 25 30

Gly Val Lys Leu Pro Thr Pro Ala Ala Pro Gly Pro His Asn Ser Ser
35 40 45

Arg Gly Gln Arg Asn Arg Arg Ala Phe Gln Gly Pro Glu Glu Thr Gly
50 55 60

Thr Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Asn Ala
65 70 75 80

Leu Glu Glu Lys Glu Asn Lys Ile Val Val Arg Gln Thr Gly Tyr Phe
85 90 95

Phe Ile Tyr Ser Gln Val Leu Tyr Thr Asp Pro Ile Phe Ala Met Gly
100 105 110

His Val Ile Gln Arg Lys Lys Ile His Val Phe Gly Asp Glu Leu Ser
115 120 125

Leu Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Lys Thr Leu Pro
130 135 140

Asn Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp
145 150 155 160

Glu Ile Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Arg Asn
165 170 175

Gly Asp Asp Thr Phe Phe Gly Ala Leu Lys Leu Leu
180 185

<210> 3236
<211> 243
<212> PRT
<213> Macaca fascicularis

<400> 3236

Lys Asp Arg Lys Leu Leu Ala Ala Ala Leu Leu Leu Ala Leu Leu Ser
1 5 10 15

Cys Cys Leu Met Val Val Ser Phe Tyr Gln Val Ala Ala Leu Gln Gly
20 25 30

Asp Leu Ala Ser Leu Arg Ala Glu Leu Gln Gly His His Ala Glu Lys
35 40 45

Leu Pro Ala Arg Ala Arg Ala Pro Lys Ala Gly Leu Gly Glu Ala Pro
50 55 60

Ala Val Thr Ala Gly Leu Lys Ile Phe Glu Pro Pro Ala Pro Gly Glu
65 70 75 80

Gly Asn Ser Ser Gln Ser Ser Arg Asn Lys Arg Ala Ile Gln Gly Ala
85 90 95

Glu Glu Thr Val Ile Gln Asp Cys Leu Gln Leu Ile Ala Asp Ser Glu
100 105 110

Thr Pro Thr Ile Gln Lys Gly Ser Tyr Thr Phe Val Pro Trp Leu Leu

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        115                 120                 125

Ser Phe Lys Arg Gly Ser Ala Leu Glu Glu Lys Glu Asn Lys Ile Leu
    130                 135                 140

Val Lys Glu Thr Gly Tyr Phe Phe Ile Tyr Gly Gln Val Leu Tyr Thr
145                 150                 155                 160

Asp Lys Thr Tyr Ala Met Gly His Leu Ile Gln Arg Lys Lys Val His
                165                 170                 175

Val Phe Gly Asp Glu Leu Ser Leu Val Thr Leu Phe Arg Cys Ile Gln
            180                 185                 190

Asn Met Pro Glu Thr Leu Pro Asn Asn Ser Cys Tyr Ser Ala Gly Ile
        195                 200                 205

Ala Lys Leu Glu Glu Gly Asp Glu Leu Gln Leu Ala Ile Pro Arg Glu
    210                 215                 220

Asn Ala Gln Ile Ser Leu Asp Gly Asp Val Thr Phe Phe Gly Ala Leu
225                 230                 235                 240

Lys Leu Leu
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<210> 3237
<211> 219
<212> PRT
<213> Macaca mulatta

<400> 3237

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Tyr Gln Val Ala Ala Val Gln Gly Asp Leu Ala Ser Leu Arg Ala Glu
1               5                   10                  15

Leu Gln Ser His His Ala Glu Lys Leu Pro Ala Arg Ala Arg Ala Pro
            20                  25                  30

Lys Ala Gly Leu Gly Glu Ala Pro Ala Val Thr Ala Gly Leu Lys Ile
        35                  40                  45

Phe Glu Pro Pro Ala Pro Gly Glu Gly Asn Ser Ser Gln Ser Ser Arg
    50                  55                  60

Asn Lys Arg Ala Ile Gln Gly Ala Glu Glu Thr Val Ile Gln Asp Cys
65                  70                  75                  80

Leu Gln Leu Ile Ala Asp Ser Glu Thr Pro Thr Ile Gln Lys Gly Ser
                85                  90                  95

Tyr Thr Phe Val Pro Trp Leu Leu Ser Phe Lys Arg Gly Ser Ala Leu
            100                 105                 110

Glu Glu Lys Glu Asn Lys Ile Leu Val Lys Glu Thr Gly Tyr Phe Phe
        115                 120                 125

Ile Tyr Gly Gln Val Leu Tyr Thr Asp Lys Thr Tyr Ala Met Gly His
    130                 135                 140
```

Leu Ile Gln Arg Lys Lys Val His Val Phe Gly Asp Glu Leu Ser Leu
145 150 155 160

Val Thr Leu Phe Arg Cys Ile Gln Asn Met Pro Glu Thr Leu Pro Asn
165 170 175

Asn Ser Cys Tyr Ser Ala Gly Ile Ala Lys Leu Glu Glu Gly Asp Glu
180 185 190

Leu Gln Leu Ala Ile Pro Arg Glu Asn Ala Gln Ile Ser Leu Asp Gly
195 200 205

Asp Val Thr Phe Phe Gly Ala Leu Lys Leu Leu
210 215

<210> 3238
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<221> site
<222> (1)..(8)
<223> Flag Tag

<400> 3238

Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 3239
<211> 250
<212> PRT
<213> Homo sapiens

<400> 3239

Met Pro Ala Ser Ser Pro Phe Leu Leu Ala Pro Lys Gly Pro Pro Gly
1 5 10 15

Asn Met Gly Gly Pro Val Arg Glu Pro Ala Leu Ser Val Ala Leu Trp
20 25 30

Leu Ser Trp Gly Ala Ala Leu Gly Ala Val Ala Cys Ala Met Ala Leu
35 40 45

Leu Thr Gln Gln Thr Glu Leu Gln Ser Leu Arg Arg Glu Val Ser Arg
50 55 60

Leu Gln Gly Thr Gly Gly Pro Ser Gln Asn Gly Glu Gly Tyr Pro Trp
65 70 75 80

Gln Ser Leu Pro Glu Gln Ser Ser Asp Ala Leu Glu Ala Trp Glu Asn
85 90 95

Gly Glu Arg Ser Arg Lys Arg Arg Ala Val Leu Thr Gln Lys Gln Lys
100 105 110

Neuberger *et al., Nature 314*:268 (1985). In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0231] The antibodies of the present invention may be monovalent, bivalent, trivalent or multivalent. For example, monovalent scFvs can be multimerized either chemically or by association with another protein or substance. An scFv that is fused to a hexahistidine tag or a Flag tag can be multimerized using Ni-NTA agarose (Qiagen) or using anti-Flag antibodies (Stratagene, Inc.).

[0232] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a BLyS polypeptide, or fragment thereof, or may be specific for both a BLyS polypeptide, or fragment thereof, and a heterologous epitope, such as a heterologous polypeptide or solid support material. See, *e.g.*, PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, *et al.*, J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny *et al.*, J. Immunol. 148:1547-1553 (1992).

[0233] The antibodies of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may bind immunospecifically to murine BLyS (e.g., a polypeptide having the amino acid sequence of human BLyS (SEQ ID NOS:3228 and/or 3229) or BLyS expressed on human monocytes; murine BLyS (SEQ ID NOS:3230 and/or 3231) or BLyS expressed on murine monocytes; rat BLyS (either the soluble forms as given in SEQ ID NOS:3232, 3233, 3234 and/or 3235 or in a membrane associated form, *e.g.*, on the surface of rat monocytes); or monkey BLyS (e.g., the monkey BLyS polypeptides of SEQ ID NOS:3236 and/or 3237, the soluble form of monkey BLyS, or BLyS expressed on monkey monocytes), preferably the antibodies of the invention bind immunospecifically to human BLyS. Preferably, the antibodies of the invention bind immunospecifically to human and monkey BLyS. Also preferably, the antibodies of the invention bind immunospecifically to human BLyS and murine BLyS. More preferably, antibodies of the invention, bind immunospecifically and with higher affinity to human BLyS than to murine BLyS.

[0234] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, antibodies of the present invention cross react with APRIL (SEQ ID NO:3239; GenBank Accession No. AF046888; J. Exp. Med. 188(6):1185-1190; PCT International Publication WO97/33902). In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under hybridization conditions (as described herein).

[0235] In preferred embodiments, the antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), immunospecifically bind to BLyS and do not cross-react with any other antigens. In more preferred embodiments, the antibodies of the invention immunopecifically bind to BLyS and do not cross-react with TRAIL, APRIL, Endokine-alpha, TNF-alpha, TNF-beta, Fas-L or LIGHT.

[0236] The present invention also provides for a nucleic acid molecule, generally

[0237] isolated, encoding an antibody of the invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof). In one embodiment, a nucleic acid molecule of the invention encodes an antibody comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the

VH domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR1 having an amino acid sequence of any one of the VH CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR2 having an amino acid sequence of any one of the VH CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VH CDR3 having an amino acid sequence of any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding antibodies that immunospecifically bind BLyS and comprise, or alternatively consist of, fragments or variants of the VH domains and/or VH CDRs are also encompassed by the invention.

[0238] In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR1 having amino acid sequence of any one of the VL CDR1s referred to in Table 1. In another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR2 having an amino acid sequence of any one of the VL CDR2s referred to in Table 1. In yet another embodiment, a nucleic acid molecule of the present invention encodes an antibody comprising, or alternatively consisting of, a VL CDR3 having an amino acid sequence of any one of the VL CDR3s referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind BLyS and comprise, or alternatively consist of, fragments or variants of the VL domains and/or VLCDR(s) are also encompassed by the invention.

[0239] In another embodiment, a nucleic acid molecule of the invention encodes an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), comprising, or alternatively consisting of, a VH domain having an amino acid sequence of any one of the VH domains referred to in Table 1 and a VL domain having an amino acid sequence of any one of the VL domains referred to in Table 1. In another embodiment, a nucleic acid molecule of the invention encodes an

antibody comprising, or alternatively consisting of, a VH CDR1, a VL CDR1, a VH CDR2, a VL CDR2, a VH CDR3, a VL CDR3, or any combination thereof having an amino acid sequence referred to in Table 1. Nucleic acid encoding antibodies that immunospecifically bind BLyS and comprise, or alternatively consist of, fragments or variants of the VL and/or domains and/or VHCDR(s) and/or VLCDR(s) are also encompassed by the invention.

[0240] The present invention also provides antibodies that comprise, or alternatively consist of, variants (including derivatives) of the VH domains, VH CDRs, VL domains, and VL CDRs described herein, which antibodies immunospecifically bind to BLyS. Standard techniques known to those of skill in the art can be used to introduce mutations in the nucleotide sequence encoding a molecule of the invention, including, for example, site-directed mutagenesis and PCR-mediated mutagenesis which result in amino acid substitutions. Preferably, the variants (including derivatives) encode less than 50 amino acid substitutions, less than 40 amino acid subsitutions, less than 30 amino acid substitutions, less than 25 amino acid substitutions, less than 20 amino acid substitutions, less than 15 amino acid substitutions, less than 10 amino acid substitutions, less than 5 amino acid substitutions, less than 4 amino acid substitutions, less than 3 amino acid substitutions, or less than 2 amino acid substitutions relative to the reference VH domain, VHCDR1, VHCDR2, VHCDR3, VL domain, VLCDR1, VLCDR2, or VLCDR3. In specific embodiments, the variants encode substitutions of VHCDR3. In a preferred embodiment, the variants have conservative amino acid substitutions at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants

can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind BLyS). Following mutagenesis, the encoded protein may routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to immunospecifically bind BLyS) can be determined using techniques described herein or by routinely modifying techniques known in the art.

[0241] The antibodies of the invention include derivatives (i.e., variants) that are modified, e.g., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not affect the ability of the antibody to immunospecifically bind to BLyS. For example, but not by way of limitation, derivatives of the invention include antibodies that have been modified, *e.g.*, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to, specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0242] In a specific embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH or VL domains referred to in Table 1 under stringent conditions, *e.g.*, hybridization to filter-bound DNA in 6x sodium chloride/sodium citrate (SSC) at about 45° C followed by one or more washes in 0.2xSSC/0.1% SDS at about 50-65° C, under highly stringent conditions, *e.g.*, hybridization to filter-bound nucleic acid in 6xSSC at about 45° C followed by one or more washes in 0.1xSSC/0.2% SDS at about 68° C, or under other stringent hybridization conditions which are known to those of skill in the art (see, for example, Ausubel, F.M. et al., eds. , 1989, *Current Protocols in Molecular Biology*, Vol. I, Green Publishing Associates, Inc. and John Wiley & Sons, Inc., New York at pages 6.3.1-6.3.6 and 2.10.3). In another embodiment, an antibody of the invention that immunospecifically binds to BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that

encoding one of the VH CDRs or VL CDRs referred to in Table 1 under stringent conditions, *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS, comprises, or alternatively consists of, an amino acid sequence encoded by a nucleotide sequence that hybridizes to a nucleotide sequence that is complementary to that encoding one of the VH CDR3s referred to in Table 1 under stringent conditions *e.g.*, hybridization under conditions as described above, or under other stringent hybridization conditions which are known to those of skill in the art. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0243] In another embodiment, an antibody (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VH CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical to any one of the VH CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0244] In another embodiment, an antibody of the invention (including a molecule comprising, or alternatively consisting of, an antibody fragment or variant thereof), that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least

50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL domains referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDRs referred to in Table 1. In another embodiment, an antibody of the invention that immunospecifically binds to BLyS comprises, or alternatively consists of, a polypeptide having an amino acid sequence that is at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identical, to any one of the VL CDR3s referred to in Table 1. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0245] Antibodies of the present invention (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) may also be described or specified in terms of their binding affinity for to BLyS polypeptides or fragments or variants of BLyS polypeptides (e.g., to the soluble form of BLyS and/or membrane-bound form of BLyS). In specific embodiments, antibodies of the invention bind BLyS polypeptides, or fragments or variants thereof, with a dissociation constant or K_D of less than or equal to 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M, 5 X 10^{-5} M, or 10^{-5} M. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5 X 10^{-6} M, 10^{-6} M, 5 X 10^{-7} M, 10^{-7} M, 5 X 10^{-8} M, or 10^{-8} M. Even more preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with a dissociation constant or K_D less than or equal to 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, 10^{-12} M, 5 X $^{-13}$ M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M. The invention encompasses antibodies that bind BLyS polypeptides with a dissociation constant or K_D that is within any one of the ranges that are between each of the individual recited values.

[0246] In specific embodiments, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an off rate (k_{off}) of less than or equal to

5×10^{-2} sec^{-1}, 10^{-2} sec^{-1}, 5×10^{-3} sec^{-1} or 10^{-3} sec^{-1}. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an off rate (k_{off}) less than or equal to 5×10^{-4} sec^{-1}, 10^{-4} sec^{-1}, 5×10^{-5} sec^{-1}, or 10^{-5} sec^{-1} 5×10^{-6} sec^{-1}, 10^{-6} sec^{-1}, 5×10^{-7} sec^{-1} or 10^{-7} sec^{-1}. The invention encompasses antibodies that bind BLyS polypeptides with an off rate (k_{off}) that is within any one of the ranges that are between each of the individual recited values.

[0247] In other embodiments, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an on rate (k_{on}) of greater than or equal to 10^3 M^{-1} sec^{-1}, 5×10^3 M^{-1} sec^{-1}, 10^4 M^{-1} sec^{-1} or 5×10^4 M^{-1} sec^{-1}. More preferably, antibodies of the invention bind BLyS polypeptides or fragments or variants thereof with an on rate (k_{on}) greater than or equal to 10^5 M^{-1} sec^{-1}, 5×10^5 M^{-1} sec^{-1}, 10^6 M^{-1} sec^{-1}, or 5×10^6 M^{-1} sec^{-1} or 10^7 M^{-1} sec^{-1}. The invention encompasses antibodies that bind BLyS polypeptides with on rate (k_{on}) that is within any one of the ranges that are between each of the individual recited values.

[0248] The invention also encompasses antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof) that have one or more of the same biological characteristics as one or more of the antibodies described herein. By "biological characteristics" is meant, the in vitro or in vivo activities or properties of the antibodies, such as, for example, the ability to bind to BLyS (e.g., the soluble form of BLyS, the membrane-bound form of BLyS, the soluble form and membrane-bound form of BLyS), and/or an antigenic and/or epitope region of BLyS), the ability to substantially block BLyS/BLyS receptor (e.g., TACI - GenBank accession number AAC51790 and/or BCMA -GenBank accession number NP_001183) binding, or the ability to block BLyS mediated biological activity (e.g., stimulation of B cell proliferation and immunoglobulin production). Optionally, the antibodies of the invention will bind to the same epitope as at least one of the antibodies specifically referred to herein. Such epitope binding can be routinely determined using assays known in the art.

[0249] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that neutralize BLyS or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv referred to in Table 1, more

preferably having an amino acid sequence contained in SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908, and even more preferably having an amino acid sequence contained in SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885 as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "neutralizes BLyS or a fragment thereof" is meant an antibody that diminishes or abolishes the ability of BLyS to bind to its receptor (e.g., TACI and BCMA) to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLyS receptor signalling cascade. In one embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that neutralizes BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0250] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that inhibit (i.e., diminish or abolish) BLyS mediated B cell proliferation as determined by any method known in the art such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, 1886 – 1908, and even more preferably having an amino acid sequence SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908, as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that inhibits BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0251] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that enhance the activity of BLyS or a fragment thereof, said antibodies comprising, or alternatively consisting of, a portion (*i.e.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908, and preferably having an

amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 – 1885, as disclosed in Table 1, or a fragment or variant thereof. By an antibody that "enhances the activity of BLyS or a fragment thereof" is meant an antibody increases the ability of BLyS to bind to its receptor (e.g., TACI or BCMA), to stimulate B cell proliferation, to stimulate immunoglobulin secretion by B cells, and/or to stimulate the BLyS receptor signalling cascade. In one embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that enhances BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that enhances the activity of BLyS or a fragment thereof, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0252] The present invention also provides for antibodies (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that

stimulate BLyS mediated B cell proliferation as determined by any method known in the art, such as, for example, the assays described in Examples 21 and 22, *infra*, said antibodies comprising, or alternatively consisting of, a portion (*e.g.*, a VH domain, VL domain, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, or VL CDR3) of an scFv having an amino acid sequence of SEQ ID NOS:834 - 872, 1570 - 1595, or 1886 – 1908, and even more preferably having an amino acid sequence of SEQ ID NOS:1 - 46, 321 - 329, 1563 - 1569, or 1881 - 1885 as disclosed in Table 1 or a fragment or variant thereof. In one embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL domain contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In a preferred embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VH CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. In another preferred embodiment, an antibody that stimulates BLyS mediated B cell proliferation, comprises, or alternatively consists of, a polypeptide having the amino acid sequence of a VL CDR3 contained in SEQ ID NOS:1 - 46, 321 - 329, 834 - 872, 1563 - 1595, or 1881 – 1908 as disclosed in Table 1, or a fragment or variant thereof. Nucleic acid molecules encoding these antibodies are also encompassed by the invention.

[0253] The present invention also provides for fusion proteins comprising, or alternatively consisting of, an antibody (including molecules comprising, or alternatively consisting of, antibody fragments or variants thereof), that immunospecifically binds to BLyS, and a heterologous polypeptide. Preferably, the heterologous polypeptide to which the antibody is fused to is useful for B-cell function or is useful to target the antibody to B-cells. In an alternative preferred embodiment, the heterologous polypeptide to which the antibody is fused to is useful for monocyte cell function or is useful to target the antibody to a monocyte. In another embodiment, the heterologous polypeptide to which the

antibody is fused is albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-x of human serum albumin, where x is an integer from 1 to 585 and the albumin fragment has human serum albumin activity. In another preferred embodiment, antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide).

[0254] In one embodiment, a fusion protein of the invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one or more of the VH domains referred to in Table 1 or the amino acid sequence of any one or more of the VL domains referred to in Table 1 or fragments or variants thereof, and a heterologous polypeptide sequence. In another embodiment, a fusion protein of the present invention comprises, or alternatively consists of, a polypeptide having the amino acid sequence of any one, two, three, or more of the VH CDRs referred to in Table 1, or the amino acid sequence of any one, two, three, or more of the VL CDRs referred to in Table 1, or fragments or variants thereof, and a heterologous polypeptide sequence. In a preferred embodiment, the fusion protein comprises, or alternatively consists of, a polypeptide having the amino acid sequence of, a VH CDR3 referred to in Table 1, or fragment or variant thereof, and a heterologous polypeptide sequence, which fusion protein immunospecifically binds to BLyS. In another embodiment, a fusion protein

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Lys Gln His Ser Val Leu His Leu Val Pro Ile Asn Ala Thr Ser Lys
        115                 120                 125

Asp Asp Ser Asp Val Thr Glu Val Met Trp Gln Pro Ala Leu Arg Arg
    130                 135                 140

Gly Arg Gly Leu Gln Ala Gln Gly Tyr Gly Val Arg Ile Gln Asp Ala
145                 150                 155                 160

Gly Val Tyr Leu Leu Tyr Ser Gln Val Leu Phe Gln Asp Val Thr Phe
                165                 170                 175

Thr Met Gly Gln Val Val Ser Arg Glu Gly Gln Gly Arg Gln Glu Thr
            180                 185                 190

Leu Phe Arg Cys Ile Arg Ser Met Pro Ser His Pro Asp Arg Ala Tyr
        195                 200                 205

Asn Ser Cys Tyr Ser Ala Gly Val Phe His Leu His Gln Gly Asp Ile
    210                 215                 220

Leu Ser Val Ile Ile Pro Arg Ala Arg Ala Lys Leu Asn Leu Ser Pro
225                 230                 235                 240

His Gly Thr Phe Leu Gly Phe Val Lys Leu
                245                 250
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